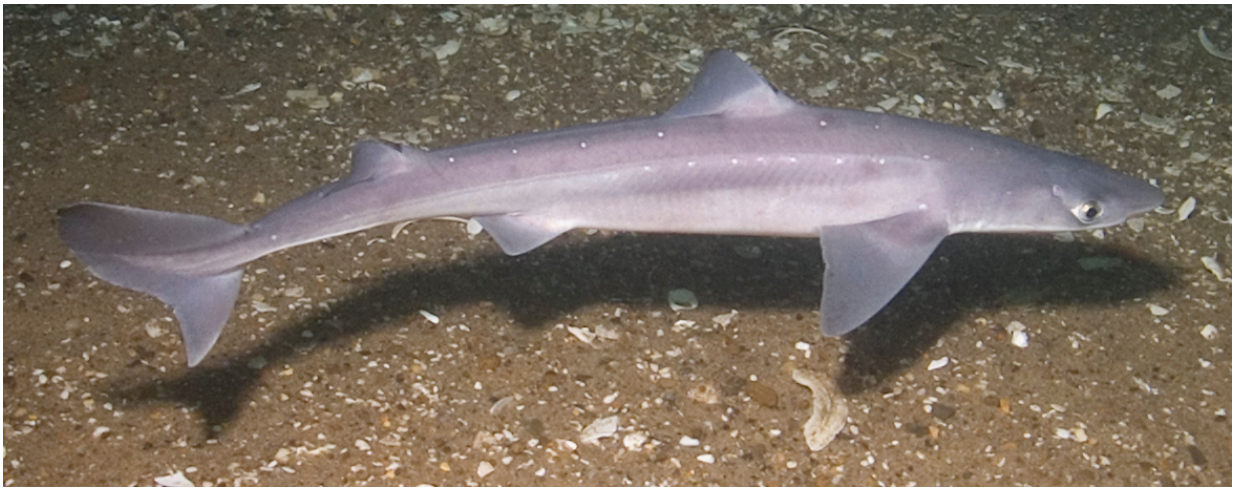
MedicalXpress

A natural compound can block the formation of toxins associated with Parkinson's disease

January 16 2017



Spiny dogfish. Credit: Doug Costa, NOAA/SBNMS

A naturally-occurring compound has been found to block a molecular process thought to underlie Parkinson's Disease, and to suppress its toxic products, scientists have reported.

The findings, although only preliminary, suggest that the compound, called squalamine, could be exploited in various ways as the basis of a potential treatment for Parkinson's Disease. The compound has previously been used in clinical trials for cancer and eye conditions in the United States, and a trial in Parkinson's Disease patients is now being planned by one of the researchers involved in the study.

Squalamine is a steroid which was discovered in the 1990s in dogfish sharks, although the form now used by scientists is a safer, synthetic analogue. To date, it has been extensively investigated as a potential anti-infective and anticancer therapy.

But in the new study, researchers discovered that squalamine also dramatically inhibits the early formation of toxic aggregates of the protein alpha-synuclein - a process thought to start a chain reaction of molecular events eventually leading to Parkinson's Disease. Remarkably, they also then found that it can suppress the toxicity of these poisonous particles.

The researchers tested squalamine in both cell cultures in the lab, and in an animal model using nematode worms. While their findings therefore only represent a step towards a treatment for Parkinson's Disease in humans, they described the results as representing significant progress.

The study was led by academics from the Centre for Misfolding Diseases, based in the Chemistry Department at the University of Cambridge in the United Kingdom, and Georgetown University and the National Institutes of Health in the United States. Scientists from the Netherlands, Italy and Spain also played key roles. The findings are published in *Proceedings of The National Academy of Sciences*.

Professor Christopher Dobson, who is one of the authors and Master of St John's College, as well as a Professor in the Chemistry Department at the University of Cambridge, said: "To our surprise, we found evidence that squalamine not only slows down the formation of the toxins associated with Parkinson's Disease, but also makes them less toxic altogether."

"If further tests prove to be successful, it is possible that a drug treating at least some of the symptoms of Parkinson's Disease could be

developed from squalamine. We might then be able to improve on that incrementally, by searching for better molecules that augment its effects."

Professor Michele Vendruscolo, from the Department of Chemistry at the University of Cambridge and a co-author, said: "This is an encouraging step forward in our efforts to discover potential drugs against Parkinson's Disease. Squalamine can prevent alpha-synuclein from malfunctioning, essentially by normalising its binding to lipid membranes. If there are going to be ways to beat the disease, it seems likely that this is one that may work."

The study stemmed from research led by Dr Michael Zasloff, professor of surgery and pediatrics at Georgetown University School of Medicine in the USA. Zasloff, who also co-authored the latest study, discovered squalamine in 1993 and has since led extensive work exploring its potential as a treatment for conditions including cancer.

In the new study, the researchers explored squalamine's capacity to displace alpha-synuclein from cell membranes - a phenomenon that was first observed in the laboratory headed by another co-author, Dr Ad Bax, in the National Institutes of Health in Bethesda, USA. This finding has significant implications for Parkinson's Disease, because alpha-synuclein works by binding to the membranes of tiny, bubble-like structures called synaptic vesicles, which help to transfer neurotransmitters between neurons.

Under normal circumstances, the protein thus aids the effective flow of chemical signals, but in some instances, it malfunctions and instead begins to clump together, creating toxic particles harmful to brain cells. This clustering is the hallmark of Parkinson's Disease.

The researchers carried out a series of experiments which analysed the

interaction between squalamine, alpha-synuclein and lipid vesicles, building on earlier work from Cambridge scientists which showed the vital role that vesicles play in initiating the aggregation. They found that squalamine inhibits the aggregation of the protein by competing for binding sites on the surfaces of synthetic vesicles. By displacing the protein in this way, it significantly reduces the rate at which toxic particles form.

Further tests, carried out with human neuronal cells, then revealed another key factor - that squalamine also suppresses the toxicity of these particles.

Finally, the group tested the impact of squalamine in an animal model of Parkinson's Disease, by using nematode worms genetically programmed to over-express alpha-synuclein in their muscle cells. As the worms develop, alpha-synuclein aggregation causes them to become paralysed, but squalamine prevented the paralysis from taking effect. "We could literally see that the oral treatment of squalamine did not allow alpha-synuclein to cluster, and prevented muscular paralysis inside the worms," Zasloff said.

Together, the results imply that squalamine could be used as the basis of a treatment targeting at least some of the symptoms of Parkinson's Disease. Zasloff says he is now planning a clinical trial with squalamine in Parkinson's Disease patients in the US.

Further research is, however, needed to determine what the precise benefits of squalamine would be - and what form any resulting drug might take. In particular, it is not yet clear whether squalamine can reach the specific regions of the brain where the main molecular processes determining Parkinson's Disease take place.

The researchers suggest that it would be particularly interesting to start

investigating the efficacy of squalamine as a means to alleviate certain symptoms. If taken orally, for instance, the compound may perhaps relieve the severe constipation many patients experience, by targeting the gastrointestinal system and affecting alpha-synuclein in the gut.

It is also conceivable that a treatment of that sort could "cascade" signals to other parts of the body. "Targeting alpha-synuclein in the gut may perhaps in some cases be sufficient to delay the progress of other aspects of Parkinson's Disease, at least for symptoms concerning the peripheral nervous system," Vendruscolo said.

"In many ways squalamine gives us a lead rather than a definitive treatment," Professor Dobson added. "Parkinson's Disease has many symptoms and we hope that either this compound, or a derivative of it with a similar mechanism of action, could alleviate at least some of them."

"One of the most exciting prospects is that, subject to further tests, we might be able to use it to make improvements to patients' lives, while also studying other compounds with the aim of developing a more powerful treatment in the future."

More information: A natural product inhibits the initiation of α-synuclein aggregation and suppresses its toxicity, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1610586114

Provided by University of Cambridge