Researchers design compound to protect against deadly toxin

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(PhysOrg.com) -- Australian researchers have discovered a new way to block the action of botulinum toxin, which may pave the way for more effective treatments of the life-threatening disease botulism.

A team comprising scientists from the Queensland Brain Institute (QBI), the University of Newcastle and the Children's Medical Research Institute have found a novel way of blocking the update of the toxin using a new class of drug called dynamin inhibitors.

“We have designed and tested a new molecule called Dyngo-4a which prevents botulinum toxin from entering nerve cells,” explains QBI Associate Professor Fred Meunier, who led the study.

“Dyngo-4a works by blocking the action of a protein called dynamin which plays a key role in controlling how most molecules can enter nerve cells.”

Botulism is a rare but potentially fatal condition that involves progressive weakness.

It is caused by botulinum toxin, which is made by the Clostridium botulinum bacterium found naturally in soil, sediments, raw foods (including seafood) and honey.

As terrorists have also attempted to use botulinum toxin as a bioweapon, development of more effective treatments to counter this type of health

threat is a high priority for countries such as the United States.

“The toxin that causes botulism is one of the most deadly agents known – it's been estimated that a single gram of it in crystalline form could kill more than one million people if distributed evenly,” Associate Professor Meunier says.

Currently, the only known treatment for botulism is antibodies that bind some of the toxin before it reaches nerve cells.

Dyngo-4a significantly delayed the onset of paralysis, botulism's most lethal symptom, by more than 30 per cent, adds Associate Professor Meunier.

“This is significant because it may provide extra time for antibodies to take effect and minimize symptoms,” he says.

“Our research is the first to identify the protein dynamin as a suitable drug target for preventing botulinum toxin entering nerve cells throughout the body.”

According to Professor Phil Robinson, Head of the Cell Signalling Research Unit at the Children's Medical Research Institute, botulinum toxin, like anthrax, is a biological agent of international concern because it has the potential to be used as a deadly weapon and to be a serious threat to public health.

The World Health Organisation notes that, while rare, botulism infections can be fatal in 5 to 10 per cent of cases.

Each year, several hundred children around the world die from botulism.

“Current treatment options for botulism are expensive and not readily

available to the public," explains Professor Robinson.

"Therefore any new developments that could lead to improved treatment options and be more widely accessible, particularly in large scale bioterrorism situations, are very welcome."

Dyngo-4a was designed by the Medicinal Chemistry team of Professor Adam McCluskey at the University of Newcastle.

The research may also have much broader implications, with the new findings potentially being useful to develop these compounds further for a range of other serious infections.

Dyngo-4a and other dynamin inhibitors are currently undergoing early stage laboratory testing for their suitability as potential therapeutics for a range of diseases.

"Our discovery not only opens up the possibility of better treatments for botulism, it also provides a new starting point for investigating potential treatments for other infectious diseases which use the same pathway to enter nerve cells in the body," Professor Robinson says.

The next steps for the research team will be to test the efficacy of higher doses of Dyngo-4a and determine the window of opportunity for treatment following exposure to botulinum toxin.

The research is published online (August) in the international *Journal of Biological Chemistry*.

Provided by University of Queensland

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