Compounds show significant promise against potential bioweapon toxins

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Because of the high cost and limited applicability of currently available treatments, the newly identified compounds have the potential to fill the existing therapy gap and to provide protection against a bioterrorism attack using the toxin.

The study is being published the week of February 5 in an online edition of the *Proceedings of the National Academy of Sciences*.

"Our study is an important milestone in the fight against biological terrorism," said Kim Janda, a Scripps Research scientist who led the study. "These small molecules are the first to show efficacy against this neurotoxin in animal models. Equally important, both have surprisingly simple structures, so their biological activity can be readily optimized. With their different modes of action, they could easily be developed as part of a potent 'cocktail' therapy."

Janda said he expects to develop more small molecule candidates as potential botulism treatments.

Botulinum neurotoxins, which cause the disease botulism, are some of the most toxic substances known to scientists. One subtype, botulinum neurotoxin A, is a 100 billion times more potent than cyanide and relatively easy to produce, making it a potential biological weapon.

Using a multifaceted screening approach, Janda and his colleagues identified the two compounds and tested their efficacy in both cell-based

assays and in mice exposed to the toxin.

One compound extended survival time by 36 percent (from 484 minutes to 659 minutes) a remarkable achievement considering its simple structure. Moreover, 16 percent of the animals treated with the second molecule survived with no obvious symptoms of botulism. No significant side effects were observed with either molecule.

Janda pointed out that the two compounds showed surprisingly little activity in cellular assays, suggesting that these standard cell-based screening methods may miss promising therapeutic candidates.

"Our study showed no correlation between cellular activity and in vivo efficacy," Janda said, "which is highly unusual. Clearly, cell-based assays do not provide all the necessary information—animal-based studies are still an essential part of the discovery process. These findings validate our multidisciplinary screening approach to identify unrecognized chemical structures as potential treatments."

While research efforts aimed at finding treatments for bioterrorism agents have increased dramatically since September 11, 2001, remarkably few have emerged. There are currently no small chemical molecules approved for treatment of botulism.

Botulism is a serious but extremely rare illness. There are seven related botulinum neurotoxins (A through G), although each acts differently and only four attack humans. The toxins kill through paralysis of the respiratory muscles. After attaching themselves to receptors on the neuronal surface—primarily muscle controlling motor neurons activated by acetylcholine, a neurotransmitter—the toxins block the release of acetylcholine proteins, inducing paralysis. Approximately 110 cases of botulism are reported each year in the United States.

Source: Scripps Research Institute