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Researchers create compounds that boost antibiotics' effectiveness

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Inhibitor compounds developed by UC Irvine structural biologists and Northwestern University chemists have been shown to bolster the ability of antibiotics to treat deadly bacterial diseases such as MRSA and anthrax.

The discovery by UC Irvine's Thomas Poulos and Northwestern's Richard Silverman builds on previous work in which they created compounds that inhibit an enzyme called neuronal nitric oxide synthase. These have demonstrated the potential to treat neurodegenerative diseases by blocking overproduction of cell-killing nitric oxide within neurons.

Now the researchers are learning that the compounds may have another important function. After Poulos and Silverman read a study suggesting that nitric oxide synthase helped pathogenic bacteria resist antibiotics, their laboratory teams paired the inhibitor compounds with currently used antibiotics to see if they could suppress NOS – and increase the antibiotics' effectiveness.

"We found that NOS inhibitors were extremely successful at inhibiting neurodegeneration in an animal model, and if they could be successful combating other diseases, we wanted to identify that as quickly as possible to help other people," said Poulos, Chancellor's Professor of biochemistry, chemistry and pharmaceutical sciences at UC Irvine.

The researchers tested their compounds on Bacillus subtilis,

nonpathogenic bacteria very similar to Staphylococcus aureus (known as MRSA), and Bacillus anthracis, which causes anthrax. Bacteria treated with the NOS inhibitors and an antibiotic were killed off more efficiently and completely than bacteria treated with only an antibiotic. The scientists then compared the three-dimensional structure of the inhibitors bound to the bacterial NOS with those bound to the neuronal NOS and determined that they bonded quite differently.

"Now that we know which region of the NOS to target, we should to be able to develop compounds that selectively bind to bacterial NOS," Poulos said, adding that his team will also need to try out those compounds in animal models.

More information: The study is published in the Oct. 31 issue of *Proceedings of the National Academy of Sciences*.

Provided by University of California, Irvine