Researchers Find How Some Antibiotics Kill Bacteria

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Researchers have uncovered how members of one family of antibiotics kill bacteria that make people sick.

This new knowledge may help drug developers make slight changes to these antibiotics to make them more effective against drug-resistant strains of bacteria, said Irina Artsimovitch, a study co-author and an assistant professor of microbiology at Ohio State University

The antibiotics studied belong to the rifamycin family. Until now, researchers believed that these antibiotics and their derivatives (there are at least a thousand) all killed bacteria in the same way.

But the new study used recent advances in X-ray imagery to obtain the highest resolution figures ever available of how rifamycins bind to their targets. With these new images, the researchers found – for the first time - that these drugs remove a key component of the bacteria they attack. The researchers were also surprised to find that different rifamycins bring about this same result in slightly different ways.

“This is a major revision of how we thought these antibiotics functioned,” Artsimovitch said. “The new molecular details help explain why bacteria that are resistant to one kind of rifamycin antibiotic might still be sensitive to another.

“That may help to narrow down the search for new synthetic derivatives to conquer resistance altogether.”

The study appears in the current issue of the journal Cell.

Ryfamycin antibiotics are one of the first-line treatments for tuberculosis, a disease that is on the rise worldwide. The drugs are also relatively inexpensive to make, have a long shelf life and are nearly non-toxic to cells other than the pathogenic ones they target.

The problem with them, though, is the rampant development of bacterial resistance.

“There is a voluntary restriction on the use of rifamycins in treating infections other than tuberculosis and meningitis due to the fear of spread of resistant mutations,” said Vladimir Svetlov, a study co-author and a research associate in microbiology at Ohio State.

“Those mutations could render these antibiotics ineffective against most of the serious health threats that they are being used to manage,” he continued.

All rifamycins belong to one of two structural classes. The researchers used two clinically important rifamycins – rifapentin and rifabutin – that represent each structural class. They obtained samples of the antibiotics in their respective crystal structure form. Crystal structures are sets of atoms arranged in ways that are unique to a particular substance.

The researchers used a technique called X-ray crystallography to determine where individual atoms are located within a crystal structure. From this information they then created high-resolution computer models of each antibiotic, approximating what each substance looked like on the atomic level and exactly how each bound to and affected a key component of bacteria called RNA polymerase.

RNA polymerase is the machinery that keeps bacteria going – a

bacterium cannot carry out gene expression without it. Cut off gene expression and bacteria are dead. In their study, the researchers looked at the effects of rifapentin and rifabutin on E. coli RNA polymerase.

With recent advances in X-ray crystallographic studies of RNA polymerase, the researchers could determine exactly where and how both antibiotics bound to RNA polymerase in E. coli, and what it did to that polymerase as a result.

The results provide new evidence of how rifamycins inhibit pathogenic bacteria. That finding applies to all rifamycins, Artsimovitch said. The study showed that rifamyacins inhibit pathogenic bacteria by removing the crucial magnesium ion (Mg2+) from a bacterium's RNA polymerase.

"Removing this ion is like removing spark plugs from an engine," Artsimovitch said. "The car may look fine, but it won't run.

"Until we could look under polymerase's molecular 'hood' we couldn't see what the problem was," she said. "We never suspected that removing this ion was what killed rifamycin-sensitive bacteria. But the resolution of previous atomic structures wasn't sufficient enough to see that."

The higher-resolution images also showed that rifapentin and rifabutin each bind just a little differently to E. coli, but still bring about the same results.

The answer to creating a new breed of bacteria-resistant antibiotics may lie in these variations in binding.

"From these findings we can suggest how rifamycins that are currently used in therapy can be improved to be effective even against existing resistant strains of bacteria," Artsimovitch said

Rifamycins are what drug companies call “broad-spectrum antibiotics.” Not only are they effective against tuberculosis, they also act against a variety of other pathogens including Neisseria meningitidis, the bacterium that causes one form of meningitis; Helicobacter pylori, which causes stomach ulcers; and even some parasitic worms by eliminating the symbiotic bacteria parasites depend on.

“It’s the kind of drug the pharmaceutical business wants to produce,” Artsimovitch said. “They’re looking for the broadest range of antibiotics possible. Rifamycins would be ideal drugs if we could figure out how to get rid of resistance.”

Artsimovitch and Svetlov conducted the study with lead author Dmitry Vassylyev, University of Alabama at Birmingham and also with RIKEN Harima Institute in Hyogo, Japan. They also worked with other researchers from the RIKEN Harima Institute and the Structural Biology Research Center of the High Energy Accelerator Research Organization in Ibaraki, Japan.

Source: Ohio State University