Old drug may teach new tricks in treating infectious diseases, cancer

October 30 2013

Meclizine, an over-the-counter drug used for decades to treat nausea and motion sickness, has the potential for new uses to treat certain infectious diseases and some forms of cancer, according to Dr. Vishal M. Gohil, Texas A&M AgriLife Research biochemist.

"Clearly this drug has many potential new applications," Gohil said. "And now that we know its new target within the cell, we can start to explore ways of using it to treat other diseases. We can 'repurpose' this drug."

The research on meclizine appears in the current online version of the *Journal of Biological Chemistry*.

"We found a particular enzyme which is inhibited by meclizine has been proposed (in other research) to be a drug target for the treatment of many diseases, including infectious diseases like malaria and African sleeping sickness," Gohil said. "And this pathway has also been proposed to be a critical pathway for the proliferation of cancer cells."

Gohil said his research, which included collaboration with scientists at Harvard Medical School and Massachusetts General Hospital, the University of Rochester and the University of Guelph, had already shown that the drug also works in the treatment of heart attack and stroke.

Meclizine is an antihistamine, synthesized in the 1950s and later found

to be useful for treating nausea, motion sickness and vertigo.

Gohil, who also is an assistant professor of biochemistry and biophysics at Texas A&M University, said he started working on the compound when he identified it in a drug-screening experiment aimed at discovering compounds or drugs that inhibit mitochondrial respiration, a process that provides energy to cells.

Mitochondria are structures found in the cells of all eukaryotes, organisms with one or more cells containing a nuclei and organelles that perform specific tasks. Enclosed in membrane, mitochondria are responsible for supplying the cell with energy and are connected to a cell's life and death.

"When that drug screen identified meclizine, it was a bit of a surprise for us, because this compound had been in the market for several years and had never been linked to mitochondrial respiration," Gohil said. "It's a known drug, and was known to target a few of the molecules within the cell."

But unlike other classes of antihistamine, he noted, meclizine has a unique property which allows it to be used for the treatment of nausea and motion sickness, while most other antihistamines cannot.

"So there was this unique thing about this particular antihistamine," Gohil noted. "And it is well-tolerated so the toxicological profile is very acceptable, so it doesn't have to be sold under strict regulations."

"With that kind of profile, when we saw it in our drug screen we got excited about it because we could see that it decreases cellular oxygen consumption or respiration," he said. "We started trying to figure out the mechanism and to see if it could have any clinical benefit and application."

Gohil said for certain diseases like stroke, heart attack and some neurological diseases, previous medical research has shown that if mitochondrial respiration can be turned down, it could be beneficial for treatment.

"The way many of the cells die during the heart attack or stroke is connected to mitochondrial respiration, so the idea was that if you can turn down the respiration, then it will prevent death," he said. "This is exactly what we found when used meclizine in models of heart attack, stroke and even Huntington disease. We have a drug with a known clinical use and have identified a new biochemical target within the cells, so that opens up new applications."

He said when he and colleagues started studying the mechanism of this drug in terms of how it is inhibiting mitochondrial respiration, they made a couple of fundamental observations. "First, when we add this drug to the whole cells, we see reduced respiration, not rapidly but slowly," he said.

The researchers then added the drug to isolated mitochondria, which is the main site of respiration within the cells.

"But we did not see an effect, so that gave us the idea that this drug may not be directly targeting one of the enzymes of mitochondria which are required for or participates in consuming oxygen," Gohil said. "We used that clue to figure out how non-mitochondrial pathways could be targeted by this drug."

He used an unbiased metabolic profiling approach, a new technology that gives a snapshot of metabolite levels before and after the treatment of a drug so researchers can get an idea of how this drug is perturbing these metabolites.

"Through metabolic profiling, we found one particular metabolite - phosphoethanolamine - was in fact 'going through the roof' within a few hours of the treatment," Gohil said. "We got excited about that."

He explained that phosphoethanolamine is an intermediate in a biosynthetic pathway of a common phospholipid that forms the membrane around the cells. It is present in all living matter from the lower organisms such as bacteria all the way to humans. Thus, finding that the metabolite that was elevated when cells were treated with meclizine indicated a link between this pathway, or metabolite, and respiration.

"Our research showed that if we just take this metabolite and directly add it to mitochondria, it actually inhibits the respiration," Gohil said. "The reason we could use the drug for infectious disease or cancer is not because it inhibits respiration but because it inhibits a phospholipid biosynthetic enzyme that is required to form the building blocks of membranes."

Provided by Texas A&M University