Small molecules might block mutant protein production in Huntington's disease

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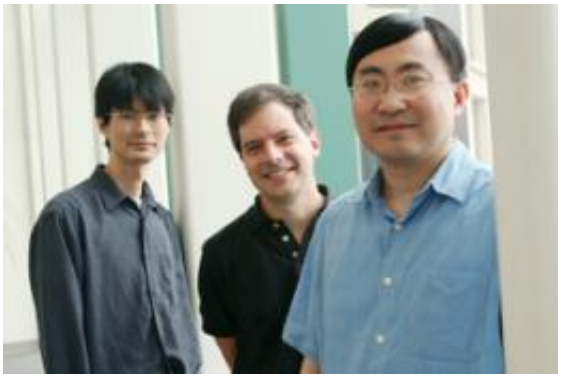

Dr. David Corey, professor of pharmacology and biochemistry (center) and from left, Dr. Masayuki Matsui, postdoctoral researcher, and Dr. Jiaxin Hu, assistant instructor in pharmacology

Molecules that selectively interfere with protein production can stop human cells from making the abnormal molecules that cause Huntington's disease, researchers at UT Southwestern Medical Center have found.

These man-made molecules also were effective against the abnormal protein that causes Machado-Joseph disease, a neurological condition similar to Huntington's.

The work has been done only in cultured cells, and it will take years before the effectiveness of this process can be tested in patients, the

researchers cautioned.

"I wouldn't want to give Huntington's patients or gene carriers any false hope, but I am excited about where this work might go in the future," said Dr. David Corey, professor of pharmacology and biochemistry at UT Southwestern and senior author of the study, which appears online May 3 in Nature Biotechnology.

The researchers' approach relies on interfering with the steps by which genetic information in cells is "translated" from DNA to make proteins, which carry out vital biological functions.

Huntington's and Machado-Joseph are fatal inherited diseases caused by abnormal repeats of a small segment in a person's DNA, or genetic code, represented by the letters CAG. These mutations result in the body producing malfunctioning proteins that cause the diseases. The more repeats, the worse the disease, and the earlier in life it appears. A person with the disease carries one normal copy of the gene and one mutated copy in his or her cells.

In Huntington's, this CAG repeat occurs in a gene called huntingtin, and in Machado-Joseph, it occurs in a gene called ataxin-3. A person with Huntington's can have up to 100 CAG repeats. CAG repeats are involved in several other neurodegenerative diseases, including Fragile X syndrome, the most common form of mental retardation, and myotonic dystrophy.

While these genes are best known for the devastating effects of their mutated forms, their normal forms are essential for embryonic development, nerve function and other bodily processes. Any treatment that interferes with the mutant forms must leave the normal forms as unaffected as possible, Dr. Corey said.

"Attempting to intervene is very risky, but because the problem is important, it's worth doing," he said.

In the current study, the researchers created short lengths of molecules that resemble ribonucleic acid (RNA), the chemical cousin of DNA. These mimics, called PNAs and LNAs, were specifically designed to bind to CAG repeats, preventing cells from creating the abnormal proteins. The researchers also designed short lengths of RNA called small interfering RNA, or siRNA, to interfere with CAG repeats.

In cells from Huntington's patients, the PNAs, LNAs and siRNAs decreased the amount of mutant protein produced, in some cases up to 100 percent. The effect was greatest when the compounds interfered with long lengths of CAG repeats; the effectiveness varied, however, among cells taken from different patients.

Some forms of these compounds left the normal forms of huntingtin and ataxin-3 proteins undisturbed, but other compounds partly or completely blocked their formation. In some cells, some of the RNA mimics drastically cut the production of both mutant and normal proteins - an undesirable effect, Dr. Corey said.

These findings indicate that further tweaking of the molecular structures of the RNA mimics will be needed to minimize the effects on normal proteins.

"It is encouraging that small chemical changes could substantially enhance selectivity," Dr. Corey said. "If we can test a handful of compounds and identify better ones, we have reason to believe that more testing will continue to produce significant improvement."

Because this study was done in cultured cells, and not in whole animals or humans, it does not indicate how much of the abnormal proteins must

be blocked to treat the disease effectively, he said. "Fifty percent inhibition might be enough, but that remains to be determined," Dr. Corey said.

In future studies, the researchers plan to try these RNA mimics in whole animals, using several different mutations of the genes.

Laurie Tompkins, who oversees neurogenetics grants at the National Institutes of Health's National Institute of General Medical Sciences, said the ability to control individual genes makes this work stand out.

"By exploiting processes that occur in normal cells, Dr. Corey has come up with a clever way to do this that may well lead to new ways to combat Huntington's and other related diseases," she said.

Source: UT Southwestern Medical Center (news : web)