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UCSF STUDY FINDS TWO OLD DRUGS MAY HELP FIGHT PRION DISEASES

UCSF researchers have determined that two drugs currently approved to treat either malaria or certain psychotic illnesses are effective in treating mouse cells infected with the infectious protein known as the prion (PREE-on). Prions cause new variant Creutzfeldt-Jakob disease, the human equivalent of "mad cow disease," as well as numerous other rare neurodegenerative diseases in animals and humans.

Because the drugs have long been used, are known to cross the difficult-to-penetrate "blood-brain barrier," and caused a dramatic response in the cells, the UCSF researchers advocate the immediate establishment of clinical trials to investigate the efficacy of the drugs in patients dying of prion diseases. Prion diseases are relentless and uniformly fatal.

The researchers report their findings and their recommendation for clinical trials in the August 14 issue of *Proceedings of the National Academy of Science (PNAS)*.

"It's a big leap from findings in cell culture to those in humans, and we do not know if we will see a favorable response in humans. But the results we saw, in a cell model we consider valid, make this lead worth pursuing immediately," said the lead author of the study, Carsten Korth, MD. Korth is a postdoctoral scholar in the UCSF laboratory of senior author Stanley B. Prusiner¹, MD, UCSF professor of neurology and biochemistry and director of the UCSF Institute for Neurodegenerative Diseases.

UCSF neurologists, in collaboration with the researchers, are in the final stages of developing a clinical trial² to test the efficacy of the two drugs in the treatment of Creutzfeldt-Jakob disease (CJD) and other prion diseases. The drugs -- quinacrine and chlorpromazine -- will be tested separately and in combination. The researchers hope to begin enrolling patients later this year.

The trial will be the first to test the effectiveness of drugs to treat human prion diseases³, which can arise spontaneously, be inherited through a genetic mutation or develop through infectious transmission. (Infection can occur from ingestion of prion-contaminated meats, contamination through biological and pharmaceutical products and, as seen in the past, from cannibalism.).

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The study

The prion (PrP^{SC})⁴ is an infectious form of a normal protein, known as the cellular prion protein (PrP^C), which exists in a healthy state in humans and many animals. The protein only becomes lethal when the tendril-like spirals that make up a portion of the protein molecule lose their normal conformation and flatten into so-called beta sheets. Once this process occurs, the misformed prion protein latches on to the spiral tendrils of other prion proteins and untwists them into flat sheets, like a wrestler pinning down an opponent.

The body probably regularly clears misfolded prion proteins from the brain's nerve cells. But when clearance doesn't occur, the deadly prion moves from one nerve cell to the next, relentlessly pinning and flattening other prion proteins as it goes. The accumulation of the flattened beta sheets within prion proteins leads to structural damage in the nerve cells that ultimately causes cell degeneration. This degeneration is seen in the tell-tale spongy appearance of affected brain tissue – thus the alternative name for prion diseases: transmissible spongiform encephalopathies.

While each prion strain contains a different protein conformation, each leads inexorably, if slowly, to dementia, paralysis and, ultimately, death.

In their study of mouse cells infected with prions, the UCSF researchers determined that quinacrine, approved to treat malaria and giardiasis, and chlorpromazine, approved to treat schizophrenia and other psychotic conditions, inhibit the conversion of normal prion protein into the disease-causing form. In other words, through biochemical analysis, the researchers determined that the drugs “cured” the infected cells.

To confirm that the mouse cells were, in fact, clear of prions, the researchers discontinued treatment of the cells with quinacrine or chlorpromazine. Prion infection did not reappear during a three-week period, considered the threshold in the cell model for a cure of prion disease.

Quinacrine was 10-fold more potent than chlorpromazine in the cell model of prion disease. However, for treating patients, chlorpromazine could prove more useful, says Korth, because it crosses the blood-brain barrier more readily and therefore could provide a higher dose of the drug in the brain.

The mouse cells used in the study were neuroblastoma cells, cancer cells that, by definition, multiply perpetually. These cells have been the basis of some prion studies for more than a decade, because they are susceptible to prion infection and have been proven legitimate indicators of the response of animals to prion infection. Whether the drugs will have any effect in patients with prion diseases remains to be seen.

In the upcoming UCSF clinical trial, the first question will be whether the drugs – either individually or in combination – have an effect against prions in patients with advanced disease. Prion diseases incubate from three to 40 years, depending on the particular prion strain, but once symptoms arise they progress swiftly, generally causing death within six to 12 months. All of the patients treated will have late-stage disease. The drugs, rarely used any more, will be prescribed at doses similar to those used for their original applications.

In the best case scenario, the researchers said, the drugs would cure or improve the patients' condition. This achievement would indicate that the therapies were clearing infectious prions from the brain's nerve cells. It would also indicate that nerve cells were actually recovering from the severe structural damage caused by the prions.

Another possibility is that the drugs would succeed in clearing prions from brain cells, but that the nerve cells themselves would be too damaged to repair themselves. In this case, the drugs could perhaps prevent further progression of the disease, though they could also prove futile in prolonging the patients' lives.

Alternatively, the drugs could prove ineffective in patients with advanced disease, but ultimately prove effective as prophylactics in patients who are infected with prions but who do not yet show symptoms. This strategy could prove useful in people who have inherited the genetic mutation leading to infectious prion diseases, as well as in those previously exposed to prions through contamination from beef products. It could also prove useful in livestock suspected of being exposed to prion disease.

New class of drug compounds to investigate

The mechanism by which quinacrine and chlorpromazine clear prions from prion-infected mouse cells is not clear. The researchers have done experiments that indicate the drugs do not appear to bind to the infectious prion, thereby preventing transmission to normal prions.

However, while the two compounds are different in many respects, they share a structural characteristic -- a tricyclic (three-ring) scaffolding with a side chain of molecules extending off a central part of their structure. And this characteristic appears to be critical to the drugs' effects against prions.

"These tricyclic compounds, with their particular side-chain, constitute a new class of anti-prion agents. Even if quinacrine and chlorpromazine themselves do not work in the human cells, they should provide a platform from which to develop many similar compounds, some of which will undoubtedly have superior anti-prion potencies, as well as higher penetration of the blood-brain barrier. We are working on this now," said a co-author of the study, Barnaby C. H. May, PhD. May is a postdoctoral fellow in the UCSF laboratory of co-author Fred E. Cohen, MD, PhD, UCSF professor of medicine and cellular and molecular pharmacology.

A clue to several neurodegenerative diseases

Insight into the drugs' mechanisms of action against prions might offer insight into the nature of other neurodegenerative disorders -- including Huntington's disease, Parkinson's disease and Alzheimer's disease -- said senior author Prusiner, as evidence suggests that each of these diseases may also result from misprocessed or misfolded proteins.

“Identifying the mechanism through which drugs act to prevent prion replication – which causes protein misfolding – could offer insight into the mechanism by which protein misfolding occurs in other neurodegenerative diseases,” said Prusiner.

On this broader front, lead author Korth’s research may prove to have taken him on a fascinating journey into the brain. A psychiatrist by training, Korth moved to the basic sciences out of frustration that little was known about the underlying basis of such psychiatric illnesses as schizophrenia. He wanted to learn the technology used to investigate neurological conditions, and wanted to do so in a “very exciting field.”

In so doing, he moved to prion research in the Prusiner lab. In his current study, he set out by identifying classes of drugs that were known to cross the blood-brain barrier to the brain, and then tested their ability to inhibit prion formation in the cultured mouse neuroblastoma cells. He identified only one class that met both criteria: phenothiazines, a group of tricyclic drugs used to treat psychosis. He then determined that a phenothiazine containing a particular side chain structure was the most effective. This was chlorpromazine.

When he discovered that phenothiazines were derived from methylene blue, a dye used in England in the 1850s, he examined other derivatives of the dye and determined that one, quinacrine, had a similar tricyclic scaffold and the same side chain structure as chlorpromazine.

Whether further research into the surprising anti-prion effects of tricyclic compounds with the central side-chain structure will lead to novel approaches in identifying the cause of such psychotic disorders as schizophrenia remains unclear. But, says, Korth, he may find he’s come full circle.

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The UCSF Department of Neurology ranks first in National Institutes of Health grants for the fiscal year 2000 and is ranked among the top programs in the U.S. News & World Report 2001 annual survey of best hospitals.

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1. Prusiner won the Nobel Prize in Physiology or Medicine in 1997 for discovering that a class of neurodegenerative diseases known as spongiform encephalopathies was caused by prions.
2. For information regarding enrollment in the planned UCSF clinical trial for treatment of prion diseases, contact: Sunita de Turreil at 415/514-1188, at the UCSF Institute for Neurodegenerative Diseases.
3. While prion diseases have traditionally been rare in humans, they have provoked world attention in recent years as more than 105 teenagers and young adults in Europe are believed to have contracted new variant Creutzfeldt-Jakob disease (nvCJD) from eating beef from cattle with the bovine form of the condition. One in a million people each year develop a sporadic form of the condition, for which there is no known cause. Approximately 5-15% of all cases are inherited. Other infectious prion diseases include kuru, which arose among New Guinea natives

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engaged in ritualistic cannibalism, and iatrogenic CJD, caused by prion-contaminated cadaveric growth hormone and dura mater grafts. Prion diseases also develop in sheep (scrapie), deer, elk and mink.

4. The prion is unlike any other disease-causing agent. All other pathogens -- bacteria, viruses, protozoans or fungi -- contain nucleic acid that allows them to transmit their pathogenic code. The prion, in contrast, is devoid of nucleic acid, and instead is composed of amino acids, as are all proteins.

Prion image: <http://pub.ucsf.edu/imagedb/imsearch.php?iname=080920011>

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