Screen finds an antidepressant, other drugs, opens possibility of treating brain-wasting mad cow disease

September 14 2011

In a new study NYU School of Medicine researchers report that they have found several chemical compounds, including an antidepressant, that have powerful effects against brain-destroying prion infections in mice, opening the door to potential treatments for human prion diseases.

The researchers, led by Thomas Wisniewski, MD, professor of neurology, pathology and psychiatry, report their findings in today's online edition of PLoS One. Prion diseases are a family of rare progressive neurodegenerative disorders that affect both humans and animals. An unusual infectious agent, a prion—a misshapen version of a normal cellular protein—causes the fatal disorders. There are no treatments.

The researchers found that trimipramine, an antidepressant, and fluphenazine, an antipsychotic, have activity against prions. Since the drugs are already in clinical use, Dr. Wisniewski believes that doctors can test them in human patients with Creutzfeldt-Jakob disease, the most common human prion disease.

Dr. Wisniewski and his colleagues previously found 68 chemical compounds, known as styryl-based compounds, bound tightly to amyloid-beta protein deposits in the brains of people who died of Alzheimer's disease. Since the disease-causing aggregates of amyloid-beta and prion proteins are widely believed to have similar structures, his team screened

these 68 styryl-based compounds for their ability to inhibit prion infection in a standard cell culture. They found two that seemed both effective and non-toxic, and confirmed their effectiveness by showing that on average they markedly delayed the onset of symptoms in prion-injected lab mice. The styryl-based compounds also reduced the signs of disease in the mouse brains.

Dr. Wisniewski's team found similar results the antidepressant trimipramine and the anti-schizophrenia drug fluphenazine. Both are chemically related to the anti-protozoal drug quinacrine, which is known to slow prion infection in cell cultures, although it fails to protect prion-infected mice or humans. Their chemical differences from quinacrine apparently enable the two drugs to bind more tightly to toxic prion aggregates, and–like the styryl-based compounds–prevent these aggregates from assembling new copies of themselves.

"One of the trimipramine-treated mice stayed healthy throughout the 400-day study," Dr. Wisniewski says.

The National Institutes of Health funds Dr. Wisniewski's laboratory's work to develop potential prion-disease vaccines. Prion diseases in animals have been known to jump to the human population. A prion disease known as bovine spongiform encephalopathy (BSE, also known as "mad cow disease") swept through cattle in Britain in the 1980s, infected humans via beef products, and killed more than 200 people worldwide.

Currently a prion disease known as chronic wasting disease (CWD) is spreading through the deer and elk population of North America. Humans are increasingly exposed to CWD, for example by eating venison, and although CWD so far doesn't seem transmissible to humans, it has been shown to infect other primates. Dr. Wisniewski and colleagues are testing an oral vaccine for CWD in deer and elk in

Colorado.

Provided by New York University School of Medicine