Medical Xpress

New drug protects neurons in Parkinson's patients

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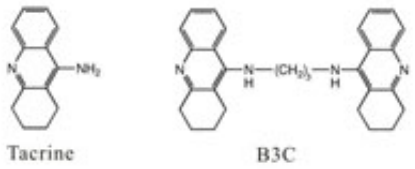

The cognitins consist of two tacrine molecules connected by a flexible chain. Bis-3-cognitin (B3C) can protect neurons from damage in an animal model of Parkinson's.

(Medical Xpress)—Scientists at Emory University School of Medicine have identified a compound that boosts levels of a survival factor in neurons threatened by Parkinson's disease.

The compound, bis-3-cognitin, could be a starting point for finding drugs that delay Parkinson's disease progression. Bis-3-cognitin appears to protect mitochondria, critical sites of vulnerability for neurons affected by Parkinson's.

In a widely used animal model of Parkinson's, bis-3-cognitin could protect neurons from damaging toxins and prevent mice from developing motor problems when it was given together with the toxin. The results were published online August 13 by the Journal of Biological Chemistry.

Zixu Mao, professor of pharmacology and neurology at Emory University School of Medicine, and his colleagues had been studying MEF2D, a protein that is vital for the survival of neurons. The first author of the paper, graduate student Lu Yao, is now at Xi'an Jiaotong University in China. Collaborators include Yifan Han and his colleagues at Hong Kong Polytechnic University.

Mao's previous research had shown that MEF2D is perturbed in the neurons of people with Parkinson's disease. The MEF2D protein is sensitive to cellular changes, such as oxidative stress, which can lead to neuron damage in Parkinson's.

"For years, we had been talking about looking for drugs that enhance MEF2D," Mao says. "The challenge was how to set up a screening system. You can search through a library of small molecules, or you can look through the literature and make a guess."

Bis-3-cognitin appears to have been a good guess, even though it was originally developed for a different purpose. The cognitins are a family of compounds derived from tacrine, the first drug approved by the FDA to treat the symptoms of Alzheimer's disease. Tacrine was eventually discontinued because of liver toxicity and other side effects. The bis-cognitins have two tacrine molecules connected by a flexible chain (see figure).

Bis-3-cognitin could protect cells in culture against damage coming from the toxin MPTP, which mimics the effects of Parkinson's, by increasing MEF2D levels in the cells' nuclei and mitochondria. Tacrine and bis-7-cognitin, which has a longer connecting chain than bis-3-cognitin, did not have the same effects.

MPTP kills dopamine-responsive neurons, which are the same cells affected in Parkinson's. In mice, the scientists gauged the toxin's

behavioral effects by measuring how long mice were able to hang on to a rotating rod, and studying their gait. Bis-3-cognitin, when given together with MPTP, could prevent motor impairment in the mice.

"We think MEF2D is not the only target of bis-3-cognitin," Mao says. "It is a potent antioxidant, for example. But MEF2D is required for the neuroprotective activity—we found that if you knock down MEF2D in cell lines, the protective effects are much weaker."

He adds that bis-3-cognitin appears to avoid the acute toxicity problems of tacrine, but more pharmacological studies of bis-3-cognitin's properties and mode of action are needed before human clinical trials.

More information: L. Yao et al. Activation of transcription factor MEF2 by bis(3)-cognitin protects dopaminergic neurons and ameliorates Parkinsonian motor defects. *J. Biol Chem.* (2012). www.jbc.org/cgi/doi/10.1074/jbc.M112.367540

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