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Study identifies small molecules mimicking key brain growth factor

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Stanford University School of Medicine researchers have identified several small molecules that mimic a key but cumbersome protein in the brain, a discovery that could open the door to new therapies for a variety of brain disorders. The protein, designated by the acronym BDNF, is known to be involved in important brain functions that include memory and learning.

"These small molecules could be the basis of drugs that provide entirely new avenues of treatment for a large number of neuropsychiatric disorders such as Alzheimer's, Huntington's and depression," said Frank Longo, MD, PhD, professor and chair of neurology and neurological sciences and senior author of a study to be published online April 19 in the Journal of Clinical Investigation.

BDNF belongs to a family of proteins called nerve growth factors, which are critical during development of the nervous system. When a growth factor binds to its receptor on the surface of a neuron, or nerve cell, it can trigger a cascade of signals inside the cell that direct the cell to survive, grow a projection extending to nearby or distant cells, or form a specialized connection with another cell that lets those two cells communicate. And in a few areas of the brain where new nerve cells can be formed, BDNF promotes this process. But its activity is diminished in certain neurodegenerative disorders, such as Huntington's disease. Even in healthy individuals, its levels decline gradually with age.

Using BDNF itself as a therapeutic drug would be tough, Longo said, as

protein drugs are not only costly to make but can't be taken orally (our digestive tracts make no distinctions between proteins in pills and proteins in Porterhouse steaks) and so would have to be injected. Even then, BDNF is very rapidly broken down in the body. "It lasts for only about a minute in the blood," said Longo, who also holds the George and Lucy Becker Professorship. Finally, the blood-brain barrier, which has evolved to protect the brain from undesirable foreign substances, would effectively bar entry to blood-borne BDNF. "So for neurologic disease, it won't reach its target."

"BDNF is a dominant and critically important molecule in the central nervous system," said neurologist Dale Bredesen, MD, a professor and founding president at the Buck Institute for Aging Research, in Novato, Calif., who was not involved in the study but is familiar with the research. "This is an important study. It's a first step in being able to develop molecules for human studies that are going to be valuable for a number of conditions, including neurodegenerative conditions and head trauma."

Possibly as important to other researchers as these molecules' therapeutic potential is the method by which they were found. The work was done in collaboration with Steven Massa, MD, PhD, a neurologist at the University of California-San Francisco and at the San Francisco Veterans Affairs Medical Center, who designed the computer search that led to the selection of potentially active molecules to be tested in the Longo laboratory. Massa shares first authorship of the study with Tao Yang, PhD, a senior scientist in Longo's lab at Stanford and, before that, at the University of North Carolina. Yang conducted many of the key bioassays to show that those compounds were, in fact, active in living systems.

First, somewhere around 1 million substances of known chemical structure were screened "in silico," i.e., via a computer search for

characteristics that indicated they were structurally similar to a particular portion corresponding to perhaps about 5 percent of the lengthy BDNF protein. This particular part of the molecule is believed critical to BDNF's ability to bind to its receptor, called TrkB, which sits on the surface of brain cells.

Massa, whose lab was responsible for the computer screening operation, said the search took only several hours - although programming the huge set of virtual compounds (which, like the books in a library, can be checked out time and again by multiple users) took a few months.

Of the million molecules tested, about 2,000 gave signs of having possible BDNF-like TrkB-binding activity. To narrow this list, the investigators used a number of rules of thumb about what kind of molecule makes a drug likely to be nontoxic, more easily absorbed and so forth. "We ended up with 14 that looked pretty good," said Longo.

But those compounds, at this point, were merely virtual, consisting of ones and zeros in electronic circuits as opposed to powders in beakers. It was necessary for the researchers to get their hands on the real ones from commercial sources. "We engaged the service of commercial small-molecule brokers, who go out and find them. These are often molecules that have no known purpose. They might have been a side reaction from a previous project, and the chemist just keeps it sitting on the shelf and there's no known use for it," Longo said.

Longo and his colleagues were able to obtain seven such molecules from commercial sources. Yang then performed laborious biological assays to see if the compounds lived up to their in-silico billing. For instance, did they keep neurons cultured in a dish from dying, as BDNF does?

"We used neurons that come from a part of a mouse's brain that is quite sensitive to neurodegenerative processes," Longo said. "Just growing in

tissue culture is challenging for them. When they're in the brain they have access to BDNF. When you pull them out of the brain and grow them in a tissue-culture dish, if you don't give them BDNF, they'll die."

Of the seven tested molecules, five had the BDNF-like ability to prevent neurons cultured in a dish from dying. The four most active are discussed in the new paper.

Importantly, these molecules bound only to TrkB. In contrast, BDNF binds to at least one other nerve-cell-surface receptor called p75. "It's thought that, when BDNF interacts with p75, it may promote pain or other deleterious functions," Longo said. "So a second advantage of our small molecules is that we're selectively targeting TrkB, which gives us an opportunity to avoid the negative effects that the natural protein might cause."

"It's very difficult to develop small molecules that mimic much larger proteins, often because the proteins and their receptors interact along very large surface areas," said Bredesen, the Buck Institute neurologist. "To be able to do that successfully, which they did, is an important step."

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