First compound for receptors in schizophrenia and Alzheimer's holds promise

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For almost 20 years, pharmacological companies have known that certain compounds that activate two specific CNS receptors, causing them to release the neurotransmitter acetylcholine, are effective in treating the cognitive and motor problems related to both schizophrenia and Alzheimer's disease (AD).

But because the compounds are "dirty" - scientific lingo for a lack of selectivity - they activate not only the essential M1 and M 4 muscarinic receptors but also the other three members of the family, designated M2, M3 and M5, resulting in unacceptable gastrointestinal and other side effects.

That may soon change, thanks to the discovery of a truly selective agonist that targets only the M1 receptor, known to be central to cognition and thus implicated in diseases like AD and schizophrenia.

On April 20, speaking at the Experimental Biology 2009 meeting in New Orleans, Vanderbilt graduate student Evan Lebois in the laboratories of Dr. David Weaver and Dr. Craig Lindsley describes the complex, labor-intensive screening and discovery process that allowed Vanderbilt scientists to pinpoint what big pharma's computers and robots could not, and the process now underway to move the compound toward becoming an effective drug to treat AD and schizophrenia. The presentation is part of the scientific program of the American Society for Pharmacology and Experimental Therapeutics.

In stage one, the search for the appropriate molecule, Dr. David Weaver, director of the Vanderbilt Chemical Biology's High-Throughput Screening facility and co-director of the Molecular Library Screening Center, painstakingly ran high-throughput screens of every compound in the molecular library to see which ones activated the M1 receptor. Most such studies are done on computers with robots and automatic scoring mechanisms. By looking with his own eyes at the waveform reactions of every compound in the library, including those already rejected by the robotic systems, Dr. Weaver identified the molecule the scientists dubbed VU019467.

It was now time for stage two, and therefore the turn of Dr. Craig Lindsley, head of Medicinal Chemistry and Director of the Vanderbilt Specialized Chemistry Center for Accelerated Probe Development. His task was to create an effective probe compound.

"There is no point optimizing a molecule's potency in vitro if it turns out not to work in vivo," says Lindsley. His probe works in both. The team now is trying the compound in mouse and rat models of Alzheimer's and schizophrenia to determine what dose range restores the appropriate level of signaling through the targeted receptor. In addition, this compound provides a tool of unprecedented selectivity that will allow the researchers to tease apart the basic role of the M1 and M4 receptors in CNS function and disease states to degree that has never before been possible.

The team hopes that within a year they will have a compound ready to license to a pharmacological company that can continue with preclinical development and then onward to human trials.

Source: Federation of American Societies for Experimental Biology (news : web)