New asthma research opposes current drug treatment

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Just when the Food and Drug Administration is reconsidering the use of stimulants to treat asthma, a new research study offers further evidence to support a University of Houston professor's theory that an opposite approach to asthma treatment may be in order.

Richard A. Bond, professor of pharmacology at the University of Houston College of Pharmacy (UHCOP), has been investigating whether beta-2 adrenoreceptor antagonist drugs (or beta blockers) ultimately might be a safer, more effective strategy for long-term asthma management than the currently used beta-2 adrenoreceptor agonists (or stimulants).

The beta-2 adrenoreceptor is a receptor found in many cells, including the smooth muscle lining the airways, and has long been a target for asthma drugs. However, a recent study shows the absence of asthma-like symptoms in a mouse model that lacks the key gene that produces the receptor. This lends further evidence to Bond's theory that questions whether the pharmaceutical industry should be working to block or inhibit the receptor instead of the current approach of chronically stimulating it to reduce asthma symptoms.

The study, "Beta2-Adrenoreceptor Signaling is Required for the Development of an Asthma Phenotype in a Murine Model," is in the current online issue of the journal *Proceedings of the National Academy of Sciences* (*PNAS*), one of the world's most-cited multidisciplinary scientific serials. A follow-up commentary by an independent scientist in

the field also will be published in the print issue of *PNAS* in February.

The timely release of this study comes on the heels of the FDA considering a renewed look at the use of long-acting beta agonist drugs (LABAs) - at least those used alone, without a steroidal component - for the management of asthma symptoms. In an FDA report released in December, an analysis of more than 100 trials on four drugs (two LABAs alone and two LABA/corticosteroid combinations) found an increased risk of hospitalization and asthma-related deaths with the LABA-only therapy. During the same month, an FDA advisory panel urged the FDA to ban the LABA-only drugs and strengthen warnings on the combination drugs.

Bond and his colleagues propose an alternative to stimulants, using antagonists (or beta blockers) instead. This approach, termed paradoxical pharmacology, suggests patients may be treated with medication that initially worsens their symptoms before eventually improving their overall health.

Beta blockers currently are contraindicated for asthma because they typically trigger bronchoconstriction, decreasing the flow of air to the lungs. Bond has suggested, however, that although beta blockers would not replace the need for emergency inhalers for acute episodes, the negative effects associated with beta blockers eventually taper off to provide long-term relief from asthma symptoms. In addition, several studies have shown chronic use of the beta-2 agonists (or stimulants) can negatively affect asthma control and airway hyperresponsiveness by desensitizing the beta-2 adrenoreceptor through regular stimulation.

In this latest study, the research team was unable to trigger the development of asthma-like symptoms in a mouse model in which the beta-2 adrenoreceptor gene had been removed as compared to the mouse model with the intact receptor gene.

"The study indicates that, with regard to developing asthma-like features, the mouse is better off without the beta-2 adrenoreceptor at all," Bond said. "It means that whether we block receptor signaling pharmacologically by using beta blockers or genetically by 'removing' the receptor, we get the same answer. The research shows that blocking or inhibiting the receptor with antagonists, instead of stimulating it with agonists, reduces the asthma-like features of the mouse model."

Bond's co-authors come from a multi-institutional research team that include current UH pharmacology graduate student Long P. Nguyen; UH pharmacology Ph.D. graduate Rui Lin; former UH post-doc fellow Sergio Parra; UH biology graduate student Ozozoma Omoluabi; Baylor College of Medicine's Dr. Nicola A. Hanania; M.D. Anderson Cancer Center's Michael J. Tuvim and Dr. Burton F. Dickey; and fellow UHCOP faculty researcher Brian J. Knoll.

With support from the Strategic Program for Asthma Research of the American Asthma Foundation, a second human clinical trial based on Bond's research is under way using the beta-blocker drug nadolol in patients with mild asthma. In the first clinical trial, sponsored by San Francisco-based Inverseon Inc., eight of 10 patients had less airway hyperresponsiveness on beta-blocker therapy at the end of the trial, although some did experience an initial negative response. (See related release at http://www.uh.edu/news-events/newsrelease.php?releaseid_int=187.)

Commenting on the results of the first clinical trial, two U.K. researchers wrote in the Jan. 10 issue of the British journal *The Lancet* that the use of beta-blocker therapy for asthma warrants serious, but careful, consideration and further investigation, including the use of specific alternative types of beta blockers.

To those ends, Inverseon, of which Bond is scientific founder, has filed

U.S. patent applications for using beta blockers to treat airway disease. Dr. William Garner, chairman of Inverseon, said the company recently received a notice of allowance - one of several procedural steps on the path to patent approval - from the U.S. Patent Office.

"The comment in *The Lancet* on Inverseon's human asthma study, combined with the notice of allowance from the U.S. Patent Office, represents important external validation of Inverseon's approach to asthma," Garner said. "We believe that our oral therapy has the potential to be a significant product for the chronic treatment of asthma."

Source: University of Houston