Key mechanisms of airway relaxation in asthma revealed in new study

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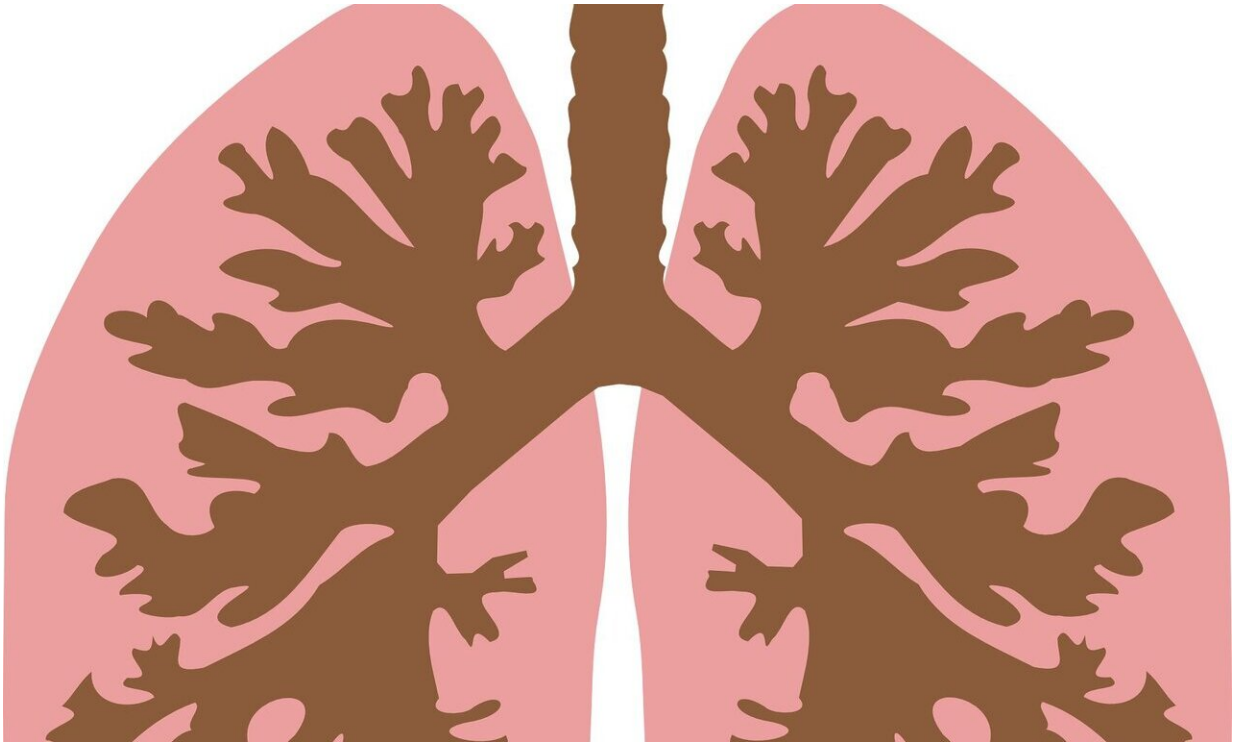

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Many therapeutics for asthma and other obstructive lung diseases target the β_2-adrenergic receptor (β_2AR), a G protein-coupled receptor (GPCR) that rapidly supports airway relaxation when stimulated. Yet, overuse of these agents is associated with adverse health outcomes, including death, which has limited their utility as frontline therapies.

Now, a mouse model study published in today's issue of *Molecular Cell*, from investigators at University Hospitals (UH) and Case Western Reserve University, identifies a novel strategy to isolate the beneficial effects of β_2AR stimulation. This suggests a new therapeutic approach to airway diseases as well as numerous other conditions involving the aberrant function of GPCRs.

"Not only is the β_2-adrenergic receptor the mainstay for keeping airways open, it's often studied as a prototype for how GPCRs work, which constitute the targets of 50% of all drugs," explained Jonathan S. Stamler, MD, President, Harrington Discovery Institute at UH, Robert S. and Sylvia K. Reitman Family Foundation Distinguished Professor of Cardiovascular Innovation, and Professor of Medicine and Biochemistry at UH and Case Western Reserve School of Medicine.

"Our discovery highlights an obvious benefit to asthma and it's exemplary of what to expect in GPCR regulation. It opens the area for broad-based research in maximizing the therapeutic benefits of GPCRs."

All GPCRs, including the β_2AR, operate via a feedback loop in which the same molecules that the receptors help generate can circle back and turn the receptors "off" or inactivate them. In the new study, the research team reveal nitric oxide to be a key molecule in the β_2AR feedback loop, showing that the production of nitric oxide after β_2AR stimulation mediates airway relaxation, but overproduction of the molecule also inactivates β_2AR, leading to bronchoconstriction.

"If you prevent that feedback, you're left with a very powerful airway relaxant that before now had not been thought to be that important in airway relaxation," said Dr. Stamler.

The study also demonstrates that mice harboring a specific mutation in the β_2AR gene that prevents nitric oxide from binding to and inactivating

the receptor are resistant to bronchoconstriction, inflammation, and asthma.

Other GPCR receptors shown in the study to be regulated by nitric oxide-based protein modification include the β_1 adrenergic receptor and the angiotensin II receptor 1.

"Nitric oxide should be thought of as a key new player in how this class of receptors works," Dr. Stamler added. "It's responsible for both the beneficial effects of the receptors and for turning them off. And if you can understand how they're being turned off—how that nitric oxide is popping on to the receptor—and you can block that, you're going to be left with a new pathway for opening airways. The next step in our research will focus on leveraging this new pathway therapeutically."

More information: Fabio V. Fonseca et al, S-nitrosylation is required for β2AR desensitization and experimental asthma, *Molecular Cell* (2022). DOI: 10.1016/j.molcel.2022.06.033

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