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Perspectives

PERSPECTIVES

β-Adrenergic Receptor Antagonism of Cholinergic Stimulation of Airway Smooth Muscle Contraction: An Old Receptor Requires a Fresh Look

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A Perspective on "M2 Muscarinic Receptor-Dependent Contractions of Airway Smooth Muscle Are Inhibited by Activation of β-Adrenoceptors"

The control of air flow resistance in the airways during breathing cycles is governed by a fine balance between the parasympathetic and sympathetic branches of the autonomic nervous system targeting airway smooth muscle cells.[1,2] During eupnea, airway smooth muscle exhibits basal tone that is controlled by postganglionic input from parasympathetic cholinergic and noncholinergic nerves and sympathetic adrenergic nerves. This basal airway smooth muscle tone is primarily driven by parasympathetic cholinergic nerves, and is opposed in most species by sympathetic nerve fibers that promote relaxation through β-adrenergic receptor signaling. There is also evidence for the involvement of parasympathetic noncholinergic postganglionic nerves, which mediate a relaxation on a slower time course than the cholinergic contraction and appear to be primarily involved in reflexively countering bronchospastic activity of the airways triggered by an insult such as coughing or exposure to a noxious substance. Autonomic regulation of basal tone during eupnea is profoundly regulated by bronchopulmonary as well as extrapulmonary afferent nerve fibers that reflexively enhance or attenuate airway smooth muscle tone by opposing or relieving postganglionic cholinergic contraction.

Although the distribution and function of parasympathetic cholinergic nerve fibers responsible for maintaining airway smooth muscle tone is widespread across species, sympathetic and noncholinergic innervation of the airways is not a common denominator and varies widely in different species. For example, sympathetic adrenergic innervation is poorly developed in human airways, but is prominent in dogs where it promotes relaxation. Mice and rats are devoid of any kind of relaxant innervation. Nevertheless, both α- and β-adrenergic receptors are expressed in human airways and can modulate smooth muscle tone when stimulated by circulating or locally released autacoids. Dysfunction of the autonomic nervous system is a major contributor to the enhanced bronchospastic activity of the airways in chronic obstructive pulmonary disease (COPD) and asthma, and blocking cholinergic muscarinic receptors and/or stimulating β-adrenergic receptors have proven efficacious in alleviating bronchospastic activity.[3,4]

Airway smooth muscle cells express both the M2 and M3 subclasses of muscarinic receptors targeted by the neurotransmitter acetylcholine (ACh).[5] The dogmatic view has been that the bronchoconstriction mediated by parasympathetic cholinergic stimulation mainly involves activation of the M3 receptor subtype, while the M2 receptor antagonizes the relaxation caused by β-adrenergic receptors but produces little direct contractile effect on airway smooth muscle. In contrast to the dogma, a study by Struckmann et al.[6] using M2, M3, or double M2/M3 receptor knockout (KO) mice showed that both receptor subtypes were required to produce the maximal bronchoconstriction elicited by ACh, albeit the M3 receptor produced greater responses. Another concept that recently emerged is the possibility that the M2 receptor may sensitize the M3 receptor yielding greater contractile responses to electric field stimulation (EFS) at low frequencies of stimulation, or to subthreshold concentrations of the muscarinic receptor agonist carbachol.[5] In a recent issue published in this journal, Alkawadri et al.[7] revisited this question in mouse airways by using a combination of pharmacological agents targeting various muscarinic and β-adrenergic

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receptor subtypes and genetic deletion of the M2 receptor subtype. They first showed that activation of M2 receptors produced more prominent responses at low frequencies (2 vs 20 Hz) and at short intervals of EFS (10 vs 100 s). Blocking M3 receptors with the selective M3 receptor antagonist 4-DAMP converted the sustained cholinergic contraction to carbachol to transient spastic mechanical events, which were abolished by the selective M2 receptor blocker methoctramine, or AFDX-116. These results indicated that although the M2 receptor may sensitize M3 receptor signaling, they also directly contribute to cholinergic bronchoconstriction, which is in agreement with muscarinic receptor KO studies in mice.[6] A very interesting and novel finding of Alkawadri et al.[7] was the demonstration that β1-adrenergic receptor stimulation with the β1-selective agonist denopamine antagonized the effects of M2 receptors to a degree that was quantitatively similar to M2 muscarinic receptor blockade. Moreover, the effects of denopamine were reduced in M2 receptor KO mice, an effect that was similar to M2 receptor inhibition. The authors reasonably argued that this finding is consistent with the idea that a major component of the relaxant effect of β1-adrenergic receptors is mediated through, and requires the prior stimulation of M2 receptors, as a direct relaxation effect would have been predicted to be augmented in the absence of the M2 receptor contractile stimulus. In support of this hypothesis and in contrast to airways, the authors showed that the relaxant effect of a β3-selective agonist on the contraction elicited by EFS in detrusor smooth muscle strips from M2 receptor KO mice was enhanced. The authors concluded that cholinergic contractions of airway smooth muscle produced by M2 receptors are specifically antagonized by β1 receptor stimulation, an effect that is considerably mitigated in M2 receptor KO mice. It will be important in the future to corroborate these findings by testing the effects of selective β1 agonists on airway smooth muscle from M3 receptor KO mice, which would be predicted to enhance, if not abolish, the cholinergic response.

The elegant study by Alkawadri et al.[7] has inspired many more questions with physiological as well as clinical implications. Is the crosstalk between β1-adrenergic and M2 muscarinic receptors mainly taking place at the receptor level through antagonism of β1-adrenergic activation of G_s-protein by M2 receptor-mediated G_i-protein signaling?[8] What is the role of global versus local compartmentalized cAMP production in this crosstalk?[9] Although high-resolution microscopy imaging will be required to answer this question, the data of Alkawadri et al.[7] suggest that the interaction is confined as cAMP production triggered by β1-adrenergic receptor stimulation produced little effect on mechanical responses elicited by the M3 receptor. It is also unclear why this antagonism was more prominent at low frequencies[5,7] and how this relates to its relevance in regulating airway resistance in vivo? A prediction would be that it would play a more significant role in eupnea but it would be attenuated during exercise.

As indicated by the authors, similar experiments will have to be replicated in human tissue samples. Targeting muscarinic and β-adrenergic receptors in mono or combined therapies using novel long-acting molecules have been the hallmark treatments to improve breathing in patients with COPD or asthma.[3,4] Given that patients with these conditions are normally prescribed with β2 receptor agonists, can novel therapies be developed on the basis of the findings by Alkawadri et al.?[7] If confirmed in human, targeting this crosstalk could pose a challenge for patients with cardiovascular diseases such as hypertension, diabetes, cardiac hypertrophy and failure, and coronary artery disease. Blocking M2 receptors, which is the main receptor involved in the regulation of pacemaker activity in the sino-atrial node, or stimulating β1-adrenergic receptors, which increases heart rate and cardiac contractile force, would be detrimental in such patients. Indeed, many of these patients benefit from treatments with β1-selective antagonists, which reduce heart rate, contraction, and afterload and contribute to preserving the oxygen reserve and overall metabolic balance of the heart.[10] Since using β1-selective antagonists is the recommended medical treatment in COPD and asthma patients when a β-blocker must be prescribed,[10] it will be of interest to review the clinical literature to determine if COPD and asthma patients medicated with a β1-selective blocker display a worse outcome than untreated patients.

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Conflict of Interest

The author declares that he has no conflicts of interest.

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