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γ-Aminobutryic Acid

Something Old, Something New for Bronchodilation

EXAGGERATED airway narrowing but impaired relaxation in diseases such as asthma is mediated by altered airway smooth muscle (ASM) response to bronchoconstrictors and bronchodilators. The considerable progress in understanding cellular mechanisms that regulate ASM contractility and hyperresponsiveness is underlined by established clinical use of β-adrenoceptor agonists, leukotriene inhibitors, and steroids. On the other hand, increasing asthma prevalence, especially in children, and advertisements for "me-too" asthma therapies targeting the same, established cellular mechanisms underscores the need for new pharmacologic treatment approaches. Although anesthesiologists have long used the bronchodilatory properties of some inhalational agents (*e.g.*, sevoflurane) and intravenous anesthetics (*e.g.*, propofol) to resolve intraoperative bronchospasm, this approach is impractical outside the operating room. In this issue of ANESTHESIOLOGY, Gallos *et al.*[1] have unveiled a new (and yet not that new!) potential target to produce bronchodilation: γ-aminobutryic acid (GABA) signaling in the airway. But it is not the known role of GABA and GABA receptors in brainstem and preganglionic cholinergic innervation to the airway that they discuss. Using an *in vitro* guinea pig airway model, they demonstrate endogenous GABA release (enhanced by agonist stimulation) that can induce bronchodilation. Furthermore, using the positive allosteric properties of propofol, they show that propofol-induced bronchodilation may be partly attributable to GABA. This paper is the latest in a series of reports by this group highlighting the role of functional GABA receptors in the airway. Although still in the investigational phase, these studies provide hope for a new approach to both outpatient and perioperative interventions to treat acute bronchoconstriction.

As an inhibitory neurotransmitter, GABA induces hyperpolarization in the central nervous system primarily *via* the ionotropic $GABA_A$ receptor and activation of chloride channels, and inhibits neurotransmitter release from primary afferent nerve terminals in the spinal cord primarily *via* the metabotropic $GABA_B$ receptor. As with other pathways initially characterized in the nervous system, there is increasing recognition that functional GABA receptors are expressed in peripheral tissues including the lung. Here is where the certainties end. Initial studies found that two GABA receptor agonists (muscimol and baclofen) did not affect basal tone in normal trachea.[2] Furthermore, GABA did not reverse acetylcholine-induced contractions, suggesting that any suppressive effect of GABA on the airway is mediated prejunctionally *via* $GABA_B$ receptor modulation of parasympathetic cholinergic input. Several groups found that GABA and the $GABA_B$ agonist baclofen protects against (neurally-derived) cholinergic bronchoconstriction, inhibits histamine-induced bronchospasm, and suppresses substance P release from primary afferents. Baclofen was also found to have antitussive effects in animals and patients with refractory cough. One study found that prolonged baclofen administration decreases excessive bronchoconstriction in spinal cord–injured patients who display unopposed cholinergic tone.[3] Interestingly, this study also suggested a postjunctional effect of GABA agonism on ASM. Although studies differed in single dose *versus* prolonged baclofen administration, they nonetheless raised the exciting possibility of using baclofen in asthma therapy. However, a small randomized, double-blind, placebo-controlled, crossover study in stable asthmatics found that 2-week oral baclofen therapy actually enhanced airway hyperresponsiveness,[4] consistent with case reports of frank bronchospasm from this therapy. However, before definite decisions could be made regarding the usability of GABA or its mimetics in diseases such as asthma, what was clearly lacking was a better understanding of complexities of GABAergic signaling in the airway: the sources of GABA, expression of GABA receptors in ASM *versus* surrounding structures, and signaling mechanisms. In this regard, the recent, elegant work in both guinea pig and human airway by Dr. Emala *et al.* is noteworthy.

Although the paper by Gallos *et al.*,[1] is fifth in the recent series by the group, it actually gets at the first question to ask (but not easy to answer) regarding GABA in the airway. Where is the GABA coming from? Unfortunately, measurement of elutes from airway preparations does not allow for determination of cellular sources of GABA. The group has previously used immunohistochemical staining to localize GABA to the interface between ASM and epithelium. While hardly definitive (given vagaries of immunostaining, especially for diffusible substances), their additional finding (in a separate paper) that airway epithelium expresses the enzyme responsible for GABA synthesis suggests a "local" source in addition to the likely presence of GABA in airway innervation.[5] The significant finding in the current paper is that cholinergic stimulation measurably enhances GABA levels. Assuming that airway epithelium actually produces and releases GABA, it still remains to be determined

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whether cholinergic (or other epithelial agonist) stimulation modulates production. If so, one can envision therapeutic interventions to enhance GABA release under opportune conditions, assuming that such interventions can be limited to the airway (*e.g.*, *via* aerosol delivery) to avoid unwanted systemic GABA effects. This also has important implications for perioperative interventions such as anticholinergics and cholinesterase inhibitors that can potentially modulate local acetylcholine action in the airway.

Regardless of the source(s) of GABA, studies by the Emala group now show that *functional* (and this is an important distinction) GABA receptors are expressed by ASM by different species, including human. Taking advantage of the controversy regarding baclofen and airway reactivity, their first study[6] looked for (and found) the metabotropic $GABA_B$ receptors in human ASM. Importantly, they found that baclofen inhibits adenylyl cyclase (and thus cyclic AMP) in ASM. Although a physiologic role for airway $GABA_B$ receptors is not established, inhibition of cyclic AMP should lead to enhanced (and not blunted) bronchoconstriction, obviously a detrimental effect. But fortuitously, as shown in another recent study,[7] it appears that ASM (including human) expresses $GABA_A$ receptors. Furthermore, selective $GABA_A$ agonists (that should activate chloride channels and hyperpolarize ASM plasma membrane) relax tachykinin and histamine-induced ASM contraction (at least in guinea pigs) and potentiate isoproterenol-induced relaxation, as recently demonstrated.[8] These novel findings were in sharp contrast to other studies showing no effect of GABA itself; however, the latter results may be attributable to opposing effects of $GABA_A$ and $GABA_B$ when both are activated. Therefore, if manipulation of the GABAergic system in the airway is to be a therapeutic reality, differential activation of receptor subtypes will be necessary, as would be targeting therapy only to ASM because $GABA_A$ receptors in airway epithelium can contribute to goblet cell hyperplasia and increased mucus production, again unwanted effects in an already narrowed airway.

The idea of using a positive allosteric agent such as propofol to unmask or enhance GABA effects is innovative. It is impressive that substantial bronchodilation is observed *in vitro* at clinically relevant propofol concentrations, a contrast to most previous findings of bronchodilation at relatively high concentrations. In their paper, Gallos *et al.*[1] suggest that propofol allosterically facilitated GABA action. However, what is not clear is why previous studies did not observe the same extent of bronchodilation at these lower propofol concentrations, assuming that GABA action also occurred in their preparations. Are there species differences in GABA or receptor distribution within the bronchial tree or differences between trachea *versus* lower order bronchi? These issues have clinical significance. For example, can the positive allosteric properties of propofol be used to enhance GABAergic suppression of cough and reflex bronchoconstriction in more proximal airways without producing bronchodilation in airway hyperresponsiveness? As an aside, if propofol facilitates GABA action, what effects does it have on other organ systems (*e.g.*, intestine or bladder) where GABAergic systems are also present? Mechanistically, are there other mechanisms by which propofol could facilitate GABAergic signaling in the airway? A tempting suggestion is that propofol by virtue of its lipid properties interferes with signaling within caveolae (ubiquitous pit-like plasma membrane structures known to contain several signaling proteins) that express GABA receptors. I look forward to future work by Dr. Emala *et al.* and others in exploring these issues; I am sure they are delving into the therapeutic potential of this underrecognized signaling mechanism in alleviating bronchospasm and airway hyperresponsiveness.

As a final note, I commend Dr. Gallos for his research efforts while in anesthesiology residency, leading to this paper and to the American Society of Anesthesiologists Research Committee awarding him First Prize in the Resident Research Essay Contest. I hope that other trainees in our specialty will emulate him in taking the path of clinically relevant translational research.

Y. S. Prakash, M.D., Ph.D. Departments of Anesthesiology and Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, Minnesota. prakash.ys@mayo.edu

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