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Baclofen and gastroesophageal reflux disease: seeing the forest through the trees

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Abstract

Baclofen has been shown to decrease reflux events and increase lower esophageal sphincter pressure, yet has never established a clear role in the treatment of gastroesophageal reflux disease (GERD). Lei and colleagues have shown in a recent elegant study that baclofen reduces the frequency and initiation of secondary peristalsis and heightens esophageal sensitivity to capsaicin-mediated stimulation. These findings may help explain both the benefit of baclofen in conditions such as rumination and supragastric belching, as well as the apparent lack of benefit of baclofen and other $GABA_B$ agonists in long-term treatment of GERD.

Gastroesophageal reflux disease (GERD) affects ~20% of American adults on a weekly basis and seems to be increasing in prevalence[1]. Proton pump inhibitors have been the mainstay of medical therapy, with an estimated direct cost of approximately $10 billion annually[2]. However, there is an increasing concern with regards to the potential adverse effects of sustained acid suppression, while ~30% of GERD patients treated with acid suppression continue to have symptoms[3]. To some extent, the reliance on acid suppression as treatment for reflux has always been somewhat counterintuitive, as overproduction of gastric acid is not believed to be the primary mechanism for symptoms in the majority of affected individuals. Numerous mechanisms have been hypothesized to result in symptom pathogenesis, including excess transient lower esophageal sphincter relaxation (TLESR), lower esophageal sphincter (LES) dysfunction or disruption, impaired esophageal clearance, mucosal abnormalities affecting barrier integrity, delayed gastric emptying, decreased fundic accommodation, esophageal dysmotility, hypersensitivity, and hypervigilance[4]. However, the dominant mechanism in the majority of patients who do not have lower esophageal sphincter disruption is believed to be excess TLESR episodes. TLESRs are vasovagal-mediated reflexes triggered by fundic distention that likely serve the teleologic purpose of venting but also allow reflux. They are mediated by several neurotransmitters and receptors, but $GABA_B$ has received the most attention and has been the primary pharmacologic target[5].

Baclofen is a $GABA_B$ receptor agonist approved for the treatment of skeletal muscle spasticity which has received significant attention due to its ability to impact TLESR response and LES parameters. In several elegant early studies, baclofen was shown to decrease TLESR episodes by ~40% and to increase postprandial LES pressure in animal models, healthy subjects, and individuals with GERD[6–8]. Mechanistically, baclofen and other $GABA_B$ agonists have been very attractive as they seem to target the underlying mechanism in the majority of affected patients and perhaps would be a more elegant approach to reflux than broad suppression of gastric acid production. However, in practice these agents have never achieved more than a fringe role in the armamentarium of reflux treatments. Clinical use of baclofen has been limited by neurologic and gastrointestinal side effects and long-term-sustained clinical responses have yet to be demonstrated. Newer $GABA_B$ agonists with less central side effects have been developed with the hope that reliable TLESR inhibition could be achieved with better tolerability. However, large randomized trials evaluating arbaclofen placarbil and lesogaberan as add-on therapy

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for symptomatic GERD patients on proton pump inhibitor therapy have been unimpressive and, to our knowledge, neither of these drugs are currently in development[3, 9, 10]. This begs the question: given the direct impact that baclofen (and other medications targeting $GABA_B$) have on the TLESR reflex, why have these agents not been more successful anti-reflux therapies?

In this issue of *Clinical and Translational Gastroenterology*, Lei and colleagues from Taiwan provide interesting insight into perhaps that exact question[11]. The investigators studied secondary peristalsis in 15 healthy volunteers after infusion of capsaicin-containing red pepper sauce following pre-treatment with both baclofen and placebo. Secondary peristalsis was triggered by injection of air via both a slow and rapid protocol and they recorded the threshold volumes required to trigger secondary peristalsis, frequency of secondary peristalsis, relevant manometric parameters, and symptom perception. Interestingly, baclofen increased the threshold volume needed to trigger secondary peristalsis with either slow or rapid air injection, decreased the frequency of secondary peristalsis and increased the intensity of reported heartburn—as compared to placebo. There were no differences noted in any of the manometric parameters of secondary peristalsis. The authors concluded that baclofen appears to have a role in inhibitory modulation of capsaicin-sensitive afferent neurons, which certainly appears to be a reasonable conclusion based on their findings. Of note, these experiments were performed in healthy volunteers and it is possible that responses may differ in a population with either GERD or esophageal dysmotility.

So often there is a focus on one mechanism of a particular agent, neurotransmitter or receptor that in the process the forest can be lost for the trees. In the case of baclofen and $GABA_B$, the promise of TLESR reduction and LES enhancement have driven production of novel agents targeting $GABA_B$ that ultimately failed due to the lack of efficacy after significant time and financial investment. Perhaps some of that failure can be attributed to the mechanisms detailed in this paper. While baclofen may reduce the number of reflux events, it also reduces frequency and initiation of secondary peristalsis which in turn may paradoxically increase the contact time between the refluxate and esophageal mucosa—perhaps mitigating the TLESR effect and explaining some of the clinical trial results. Likewise, if symptom perception is enhanced through baclofen (and presumably $GABA_B$), then this also could explain why therapy with baclofen often does not seem to result in the expected symptomatic benefit based solely on its modulation of the TLESR reflex. The paper by Lei and colleagues is a reminder to some extent that $GABA_B$ has peripheral and central effects throughout the vasovagal pathway and is not simply limited to the LES and control thereof.

By expanding our understanding of the role of $GABA_B$ in esophageal physiology, it may also be possibly to tailor the use of baclofen more effectively for those patients who might truly derive benefit. For example, baclofen has become the medication of choice for rumination, which is reasonable given that the reduction in TLESRs and enhancement of LES pressure would be beneficial whereas heightened esophageal sensitivity and reduced secondary peristalsis may not necessarily pose problems in this patient population[12]. Likewise, the reduction in initiation of secondary peristalsis to air instillation may be beneficial in patients with supragastric belching—perhaps explaining some of the benefits shown by baclofen in such patients[13]. Greater understanding of the underlying mechanisms may allow us to target baclofen selectively for specific patients in the future outside of these specific indications.

The role of transient receptor potential vanilloid-1 (TRPV1) channels also deserves thought. The mechanisms demonstrated in the study by Lei and colleagues were in the context of capsaicin administration, believed to stimulate the TRPV1 receptor. None of these neurotransmitters and receptors function in isolation and it appears that $GABA_B$ receptors and TRPV1 receptors have an interrelationship that could potentially be modulated for therapeutic gain. Is it possible for instance to produce a combination therapy that perhaps achieves the favorable TLESR modulation of baclofen while blunting hypersensitivity? Only time will tell, but for now the increased understanding of baclofen's mechanism explains the discrepancy between clinical trials and theoretical benefits, allows increasing information to tailor therapy for our individual patients and highlights the continued complexity of esophageal physiology.

Competing interests

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