CHEST

Translating Cough Mechanisms Into Better Cough Suppressants

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Chronic cough is a significant problem, and in many patients cough remains refractive to both disease-specific therapies and current cough-suppressing medicines, creating a need for improved antitussive therapies. Most patients with chronic cough also display heightened sensitivity so that they experience a persistent sense of the need to cough, and often innocuous stimuli can trigger their coughing. This hypersensitivity underpins the newly described concept of cough hypersensitivity syndrome (CHS), a term that encapsulates the notion of common underlying mechanisms producing neuronal activation, sensitization and/or dysfunction, which are at the core of excessive coughing. Understanding these mechanisms has been a focus of recent research efforts in the field in the hope that new therapies can be developed to selectively target sensitized unproductive cough while maintaining the reflexive cough essential for airway protection. However, efforts to achieve this have been slower than expected, in part because of some significant challenges and limitations translating current cough models. In this review, we summarize recent advances in our understanding of the sensory circuits innervating the respiratory system that are important for cough, how cough sensory pathways become hypersensitive, and some of the recently described neural targets under development for treating chronic cough. We present the case that better use of current cough models or the development of new models, or both, is ultimately needed to advance our efforts to translate the discovery of basic cough mechanisms into effective medicines for treating patients with chronic cough.

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Cough is a normal physiological response to airway irritation, serving a fundamental role in airway protection and the maintenance of airway patency. It can occur voluntarily or in response to an airway irritation and can be both reflexive and nonreflexive (behavioral) in nature. Although coughing itself reflects a coordinated effort of the respiratory muscles, the underlying control mechanisms are dependent on complex neurophysiological events. The neural pathways that control coughing have been the subject of intense investigation in recent years, and much is now known about how voluntary and evoked cough are generated.[1] In disease, cough can become excessive, nonproductive, and hypersensitive, occurring in response to stimuli that do not normally cause cough.[2] Accompanying cough in disease is usually a persistent and difficult to satiate urge to

ABBREVIATIONS: ATP = adenosine triphosphate; CHS = cough hypersensitivity syndrome; Nav = voltage-gated sodium; TRP = transient receptor potential

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cough—a distinct symptom that represents the perceivable sensory component of coughing.[3] This phenotype can be present in > 100 clinical conditions, and as such it is now recognized as a distinct entity in itself, referred to as chronic cough hypersensitivity syndrome (CHS).[4-6] Despite the heterogeneity in underlying diseases, enhanced sensitivity to both tussive and nontussive stimuli (known as hypertussia and allotussia, respectively) in CHS is common across diseases, indicating that hypersensitivity of the peripheral or central components of the cough neural pathway, or both, is important in the development of the disorder.[2,7] A current focus of the field is to identify the mechanisms that lead to neural activation and sensitization, as this is likely to provide novel therapeutic options for treating patients with CHS. Some progress has been made in this regard, largely from preclinical animal studies investigating the cough reflex. However, the therapeutic options for treating patients with CHS remain limited. Most current antitussive agents have been available for many decades and display poor efficacy or undesirable side effects.[8] Many offer no therapeutic value greater than a placebo. A number of new potential agents are under development, some of which have entered clinical trials with largely (but not entirely) disappointing outcomes. This raises the question, "Why have preclinical studies not been predictive of human cough in disease?" This state of the art review begins to explore this issue by presenting an update on the basic mechanisms of cough, the current state of play of novel antitussive therapies targeted at neural mechanisms, and, finally, some considerations for the use of preclinical studies in antitussive development.

Cough Neurobiology in Health and Disease

The act of coughing spans a spectrum from purely voluntary to purely reflexive (Fig 1), the former initiated by the conscious decision-making processes in the cerebral cortex and requiring no input from sensory pathways in the airways and the latter initiated by sensory pathways in the airways and not requiring central neuronal processing above the brain stem level[9] (Fig 2). Between these extremes exists coughing that is initiated from the airways but is also under behavioral modulation by the higher brain (Fig 1). With the exception of some psychiatric disorders in which cough can be purely voluntary, much of cough in disease is presumed to be evoked with varying levels of behavioral control. The airway sensory fibers that initiate coughing are all vagal in origin, with their peripheral terminals

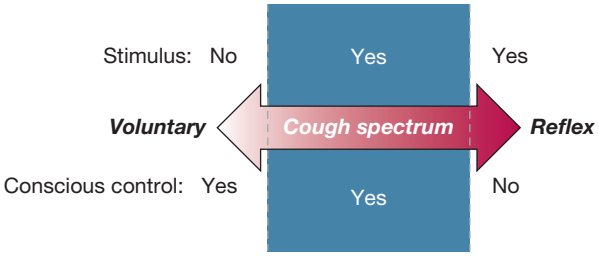

Figure 1 – *The spectrum of cough. Purely voluntary cough is consciously generated from the motor cortex in the brain independent of any peripheral sensory input from the airways. Purely reflex cough requires peripheral sensory input to the brain stem and occurs independent of any conscious control from the higher brain. This type of cough can be evoked under decerebrated or heavily anesthetized conditions and represents the basic defensive cough reflex. Between these two extremes on the spectrum (denoted by the shaded area) lays coughing that is dependent on sensory input but is under various levels of behavioral control and is able to be enhanced or suppressed consciously. Much of cough in disease likely exists within this domain, which may explain why speech therapy is an effective treatment for chronic cough.*

associated within or just below the respiratory epithelium.[1,10-12] The cell bodies of these vagal fibers are located within two anatomically and embryologically distinct vagal ganglia known as the jugular (superior) and nodose (inferior) ganglia, both of which contain heterogeneous populations of sensory neurons that monitor a wide range of physiological and noxious sensory modalities. Although most sensory neurons are somewhat polymodal in nature, two fundamentally different subsets of sensory neurons detecting chemical (chemoreceptor fibers, sometimes called nociceptors) or mechanical (low-threshold mechanoreceptor fibers, sometimes called cough receptors) stimuli exist.[1] Signals from these fibers are transmitted centrally to distinct brain stem sensory nuclei where initial processing occurs before relaying to the brain stem respiratory pattern generator to produce the cough motor pattern as well as onto higher brain regions for the perception of airway irritation allowing for behavioral modulation of coughing.[3,13] The central pathways involved in cough processing have been investigated in both animal and human studies (Fig 2). Cough-evoking chemoreceptors detect a wide range of potentially noxious stimuli, including exogenous chemicals and endogenous inflammatory molecules. The vast majority of chemoreceptors are unmyelinated (slow conducting) C-fibers, which are insensitive to lung stretch and thus are generally quiescent in the healthy respiratory system but become activated in response to tissue irritation or inflammation. The low-threshold mechanoreceptors that evoke cough are classified as myelinated (faster conducting) Aδ-fibers and are exquisitely sensitive to punctate (touchlike) stimuli, rapid reductions in airway