A streetcar named urge-to-cough

Donald C. Bolser

Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, Florida

We learn that Blanche DuBois is considerably more complex than meets the eye. So too is a recently identified sensation associated with the production of cough, known as the “urge-to-cough” (3, 4). In this issue of the Journal of Applied Physiology, Lavorini et al. (8) have investigated the influence of voluntary hyperpnea and exercise on induced cough and urge-to-cough in healthy adult humans. They show that both cough sensitivity and urge-to-cough are suppressed by voluntary hyperpnea and bicycle exercise. These investigators concluded that perception of the magnitude of urge to cough can be inhibited by sensory feedback from exercising limbs, thoracic muscles, and/or higher nervous mechanisms (presumably cortical). These results represent part of an emerging body of evidence that sensations are an important component of the cough response in the human and that these sensations can be modified by sensory feedback.

The classical view is that cough is an involuntary behavior that is primarily produced and controlled by a network of neurons restricted to the brain stem (10, 12, 13). There is strong evidence from animal models and studies in anesthetized humans supporting this concept (11, 13). However, this view must be amended to account for important suprapontine involvement in the awake human (9, 16). While it is tempting to restrict these suprapontine mechanisms to the motor cortex, a host of other cortical regions are involved in the production of coughing as well (9). Evidence in support of the involvement of brain regions related to emotion and affect in the regulation of cough can be found in a study showing that affective state can modulate the expression of this behavior. Davenport and coworkers (4) showed that anxiety-producing conditions (such as withdrawal of tobacco) can enhance urge to cough and cough responses in smokers, but the findings of Lavorini et al. (8) suggest that exercise has the opposite effect on these metrics of coughing. Presumably, the levels of exercise employed by Lavorini et al. (8) were not anxiolytic. An important difference between the two studies is that ventilation was significantly enhanced during voluntary hyperpnea and exercise (8). This difference is consistent with the presence of a complex control system that takes into account ventilatory state and demand, balancing these factors with other sensory modalities that utilize a common motor control system for airway defense and breathing. For example, cough responses and sensitivity also are decreased when ventilation is increased during systemic hypoxia in animals and humans (5, 15).

It is well known that cough can be produced or suppressed through voluntary means (6, 7). The extent to which the suppressive mechanisms actuated in the study of Lavorini et al. (8) might be mediated through control systems involved in voluntary cough is unknown. However, this issue may be testable in the human via a protocol incorporating the production of voluntary cough during exercise.

Recent evidence has shown that codeine, the gold standard cough-suppressant drug, is ineffective relative to placebo in humans with airway pathology (14). Despite ongoing efforts by pharmaceutical companies over the last several decades to discover novel and effective cough-suppressant drugs, there are no new and effective antitussives on the market. The reflex suppression of cough sensitivity and sensations demonstrated by Lavorini et al. (8) provide further evidence that endogenous inhibitory mechanisms for cough exist in the awake human. These effects are presumably mediated by central neurotransmitters/neuromodulators that could represent targets for drug discovery efforts. The experimental paradigm of Lavorini et al. (8) could be used in investigational trials designed to pinpoint the pharmacologic mechanism(s) of suppression. Trials could be designed utilizing one or more of the wealth of neuroactive drugs that are currently approved for use in humans. This approach is consistent with the current emphasis on translational research at the National Institutes of Health and is an example of “bedside to bench.” To my knowledge, no pharmaceutical company has taken this approach in discovery efforts for antitussive drugs. The most common approach used in antitussive discovery efforts is “bench to bedside” in which initial efforts begin with in vitro and in vivo animal and (sometimes human) tissue models. Reversal of this classical, but so far unsuccessful, approach will considerably expand our knowledge base of the neuropharmacology of cough in the human and may lead to the discovery of a novel and effective antitussive agent.

The results of the study of Lavorini et al. (8) are supportive of a hierarchical control system for cough that is proposed to involve brain stem and suprapontine pathways in awake humans (1, 2). This system is holarchical, meaning that it is composed of control elements that are part of a larger control matrix but each element imparts novel features to the system that are not easily predicted by knowledge of lower order components. In an imaging study, Mazzone and coworkers (9) showed that some, but not all, cortical regions that were activated during capsaicin-induced cough in the human had signal intensities that were correlated with the urge-to-cough. These findings suggest the presence of urge-specific and urge-independent elements in the suprapontine control of coughing. The manner in which these elements interact with each other, their responsiveness to sensory feedback such as that induced by Lavorini et al. (8), and their interactions with putative lower order control elements in the brain stem are currently not understood. I look forward to future studies that “challenge” the urge-to-cough to reveal these secrets and more.

REFERENCES


