RESPIRATORY REFLEXES elicited from activation of sensory endings in the lungs are responsible for performing two primary functions essential to the overall respiratory function. One is responsible for the regulation of breathing and bronchomotor tone, as well as the maintenance of homeostasis. The other is the defense reflexes that protect the lung and the rest of the body from any potential health hazards caused by inhaled irritants or toxic substances.

Like any other physiological control system, the respiratory reflexes require precise coordination and integration of the activities of three major components: the sensors, the central controller, and the effectors. The seven mini-reviews presented in this Highlighted Topic series focus on specific topics in these three areas in which interesting and important new findings have recently emerged.

In the area of airway sensors, Drs. Taylor-Clark and Undem have presented a comprehensive review of the recent advances in our understanding of the transduction mechanisms of sensory receptor activation. Many innovative studies employing modern molecular and cell biology techniques have been recently reported in other sensory systems (4, 7). These new findings offer a glimpse into the enormous potential and possibility for advancing our knowledge about the transduction properties of airway sensors. In particular, recent studies have been focused on how sensitivity and function are altered in acute and chronic pathophysiological conditions of the airways. Another interesting feature is the development of neural plasticity that may involve changes in the gene expression and protein synthesis of neuromodulators and/or ion channels in the neurons. It is certainly an important but challenging task to unravel the mechanisms regulating the changes in gene transcription that lead to the changes in neuronal sensitivity.

The anatomical evidence of the presence of clusters of neuroendocrine cells in the airways and their function of regulating the growth of developing lungs have been well recognized for decades (5). Recent investigations have begun to reveal compelling morphological evidence that the neuroepithelial bodies act as transducers or part of the sensor-nerve complex in the airways. As illustrated in the review by Dr. Adriaensen and colleagues, the neurochemical content and secretory nature of these cells, and their intimate and extensive contact with sensory endings of myelinated afferent fibers, suggest their potential role as part of the mechanoreceptor terminal units. On the other hand, the superficial location of these cells in the airway epithelium and dense distribution at the bifurcating points of the tracheobronchial tree appear to be well situated to detect inhaled irritants (5). However, other than the experimental evidence of sensitivity to hypoxia, the role and function of neuroepithelial bodies as airway sensors remain poorly understood.

Central controller plays a critical role in integrating the afferent inputs and regulating the motor outputs of the airway reflexes. Dr. Kubin and coworkers presented a detailed review of the central neural pathways in the brain stem that mediate and coordinate the cardiorespiratory reflexes elicited by activating each of the three major types of airway sensors, namely slowly adapting receptors (SARs), rapidly adapting receptors (RARs), and bronchopulmonary C fibers. Individual types of these sensors are known to project to the second-order neurons located at different sites of the nucleus of the solitary tract (NTS). Although this map describing the relative segregation of central projections of lung afferents is well accepted, it is continuously being refined as new findings emerge from the studies using various novel experimental approaches. One such challenge is a recent observation suggesting that one single vagal axon can conduct afferent activities arising from two different types of sensors or “encoders” (e.g., SAR and RAR) in the lung (11).

When the activity of airway afferents is elevated by environmental stresses or disease conditions for a sustained period of time, neural plasticity is known to develop at multiple sites along the reflex pathways. The NTS, where all the respiratory afferents converge, is a natural site for modulating the signal processing under these abnormal conditions. The activity-dependent long-term potentiation can lead to exaggerated reflex responses such as bronchospasm or uncontrollable cough. Dr. Bonham and colleagues discussed the complexity of possible mechanisms of induction and expression of plasticity at the NTS neurons after chronic exposure to inhaled irritants. These studies further provided information that may be useful in identifying potential targets of plasticity in the NTS.

The efferent output from the central controller is conducted through a number of neural pathways and activates a wide range of cells, organs, and systems. In addition to the respiratory system, some of the effectors reside in nonrespiratory organs, such as cardiovascular, renal, and endocrine systems. Dr. Canning’s review focuses on one of the most important aspects of the respiratory reflexes: the regulation of airway smooth muscle tone, which exemplifies the complexity of the centrally mediated reflex regulation of airway function. Bronchomotor tone is regulated by multiple afferent and efferent pathways, and additional factors are called into play under pathophysiological conditions, which may act on different sites of the reflex neural circuit. Similar neural pathways and mechanisms are also present in the reflex regulation of other important effectors in the airways, such as mucous glands, bronchial vessels, etc. (8).

Another important motor output driven by the airway reflexes involves the muscles that control the opening and caliber of the upper respiratory tract. The review by Drs. Bailey and Fregosi focuses on how the motor activities of these muscles are coordinated precisely and cohesively with that of the pump muscles. The reflex control of the upper airway muscles, largely in tune with the inputs from SARs, plays a crucial part in regulating the airflow and airway resistance. As the authors point out, many important questions remain to be answered, especially the roles of RARs and C fibers in regulating the motor activities of these muscles. Because dysfunction of the reflex regulation of these muscles is a major cause of the obstructive sleep apnea, a better understanding of the central signal processing and integration that orchestrate the reflex control of these muscles is certainly very important.

The two main purposes of these mini-reviews are to highlight the recent significant advances in specific areas and to identify the knowledge gaps where additional research efforts are needed. A number of very important and challenging
questions have been raised. For example, on the basis of the well-established criteria, the receptors in the lung and airways are classified into three major categories: SARs, RARs, and C fibers. However, it is also apparent that these receptors represent a heterogeneous group with diverging transduction properties and functions. In addition, many new subgroups with distinctly different functional characteristics continue to be identified (2, 3). Another issue concerns the neuroimmunological interaction. Both sensory nerves and the immune system are the major players in defending the lungs against inhaled irritants and allergens. It seems, therefore, logical to expect a close interaction between them in performing this important function. Indeed, some of these cross regulations have already been demonstrated in other organ systems; the efferent activity of the “inflammatory reflex,” mediated through the “cholinergic anti-inflammatory pathway” in the vagus nerves, inhibits cytokine release from macrophages in the gastrointestinal tract (6). In addition, certain cytokines (e.g., interleukin-1β) are actively transported across the blood-brain barrier, and various cytokine receptors are expressed in central nervous system neurons (6). Furthermore, sensory neuropeptides (e.g., tachykinins) released from C-fiber endings can exert chemotactic action on immune cells, whereas a number of mediators released from leukocytes generate potent stimulatory effects on airway afferents (1, 9, 10). Whether the neuroimmunological interaction plays a part in the development of neural plasticity in regulation of airway reflexes remains to be explored.

The new discoveries described in these reviews would not have been possible without the ground-breaking discoveries of the respiratory reflexes by many pioneering investigators in the early days, as narrated so eloquently in the Historical Perspective article by Dr. John Widdicombe, whose own life-long contributions have made immeasurable impacts on our current knowledge of airway receptors. On that note, I want to, sadly, give our tributes to the three preeminent scientists in this field who have passed away in the last several years: Dr. Giuseppe Sant’Ambrogio, Dr. John Coleridge, and Dr. Autar Paintal. To each one of them, we are indebted to their dedication and contribution to the advancement of the frontier of research in airway receptors and reflexes, which laid a solid foundation for the younger investigators to build on. Hence, it is only appropriate to dedicate this Highlighted Topic series to memory of these legendary scientists and their accomplishments.

REFERENCES