invited editorial

Invited Editorial on “Evidence that neuroepithelial endocrine cells control the spontaneous tone in guinea pig tracheal preparations”

ERNEST CUTZ AND ADELE JACKSON
Department of Paediatric Laboratory Medicine, Research Institute, Hospital for Sick Children, and University of Toronto, Toronto, Ontario M5G 1X8, Canada

A RELATIVELY RARE AND OBSCURE airway epithelial cell type, the so-called neuroepithelial endocrine (NEE) cell, has until recently been considered a morphological curiosity with undefined function. These cells, discovered over 50 years ago, were identified as argyrophilic cells distributed within the airway epithelium of human and animal lungs. Subsequent immunohistochemical investigations confirmed the presence of biogenic amine (serotonin (5-HT)) and of several peptide hormones, including bombesin, calcitonin, calcitonin gene-related peptide, CCK, Leu-enkephalin, as well as a number of neural and neuroendocrine markers (see Refs. 1, 2, and 10 for reviews). The identification of endocrine and neurallike features led to the designation of the pulmonary neuroendocrine cell (PNEC) system comprising solitary PNEC and innervated PNEC clusters, termed “neuroepithelial bodies” (NEB) (2, 6, 7). Whereas solitary PNEC and NEB exhibit identical phenotype in terms of amine, peptide, and neuroendocrine marker expression, only NEB appear to be innervated and occur exclusively within the intrapulmonary airways (7). In contrast, solitary PNEC often form thin apical or lateral cytoplasmic processes and are distributed within the epithelium lining the larynx, trachea, and bronchi, down to the bronchiole-alveolar junction (1, 2, 10).

Based on these morphological findings, it is expected that NEB signaling involves input and modulation via the central nervous system, whereas solitary PNEC may act locally on adjacent cells and/or critical anatomic structures (i.e., bronchial smooth muscle). During the past 20 years, a great deal of information on the morphology of PNEC system has been generated, but their precise function in the lung remains largely unknown, including the functional relationship between solitary PNEC and NEB.

Current consensus suggests a multifunctional role for PNEC system in mammalian lungs, with three main hypotheses advanced. First, a function of airway chemoreceptors (relevant mostly to NEB) acting as transducers of hypoxia stimulus via neural input, affecting the control of breathing and/or other pulmonary function, has been postulated (2, 6, 11). There is remarkable similarity between NEB cells and well-defined chemoreceptors, the glomus cells of the carotid body. As glomus cells, NEB cells release amine (5-HT) in response to hypoxia (3, 6); and an O₂-sensing mechanism has been demonstrated at the cellular and molecular level (15, 16). Recent studies in our laboratory have shown that NEB cells exhibit membrane properties of excitable cells, since they possess voltage-activated K⁺, Na⁺, and Ca²⁺ currents (4, 15–17). We have also shown that hypoxia (PO₂ 25–30 Torr) reversibly reduced K⁺ current, whereas Na⁺ and Ca²⁺ currents were unaffected (4, 16, 17). In related studies, we have further shown that the gating of O₂-sensitive K⁺ current may be modulated by reactive oxygen intermediates such as H₂O₂ (4, 15, 17). The evidence for this included the demonstration in NEB cells of a H₂O₂-generating NADPH oxidase (16, 18); also, diphenylene iodonium (DPI), an inhibitor of the oxidase, suppressed O₂-sensitive K⁺ current, whereas direct application of H₂O₂ augmented the K⁺ current (4, 15–17). Thus a membrane model for O₂ sensing has been proposed on the basis of an interaction between O₂-sensing protein (NADPH oxidase) and O₂-sensitive K⁺ channel (15, 17). The second hypothesis for the function of PNEC relates mostly to the developing lung and is based on known growth factor-like properties of bombesin and related peptides, highly expressed in PNEC of human fetal lung (see Ref. 14 for review). The third hypothesis postulates effects via adjacent vascular structures and/or modulation of bronchomotor tone by targeting airway smooth muscle and associated nerve endings in proximity to PNEC (6, 11). At present, there is no direct evidence in support of the latter hypothesis.

A number of studies indicate that airway epithelium can modulate the responsiveness of underlying smooth muscle in several ways; e.g., it acts as a physical or metabolic barrier by restricting the access or by inactivating potential constrictor (or relaxant) agonists to smooth muscle or nerves, or the epithelium itself secretes factors (e.g., prostaglandins and other eicosanoids, 5-HT, calcitonin gene-related peptide, cytokines, nitric oxide, epithelium-derived relaxing factor, etc.) that modulate the activity of smooth muscle (12, 13). Removal of epithelium from bronchi has been shown to increase the contractile responses evoked by acetylcholine, histamine, and 5-HT, suggesting that airway epithelial cells may generate an inhibitory signal to
decrease the responsiveness of bronchial smooth muscle to contractile agonists and augment the effectiveness of inhibitory stimuli (8). Whether these effects are specific to a particular airway epithelial cell has not been previously investigated. The following paper by Skogvall et al. (9) provides novel physiological evidence for involvement of O₂-sensing PNEC (term “NEE cell” used by the authors) in the contractility of airway smooth muscle in isolated tracheal preparations. Spontaneous tone in isolated guinea pig tracheal preparations was assessed before and after interference with NEE cell function, either via pharmacological agents or by epithelial denudation.

After removal of the epithelium, the tracheal preparations failed to develop a highly stable tone with repetitive bursts of oscillations (i.e., complex spontaneous tone) in 12% O₂ (corresponding to arterial O₂ levels) and, instead, showed a strong nonoscillating smooth tone normally observed in 94% O₂. In intact preparations, inhibition of H₂O₂ production with DPI transformed the smooth strong tone to an oscillating tone with less force in 94% O₂. In addition, exposure of intact preparations to H₂O₂ transformed the tone from a complex type to one that is strong and smooth in 12% O₂. Hence, “silencing” or “activating” O₂-sensing signal transduction in NEE cells with H₂O₂ or DPI, respectively, altered the generation of spontaneous tracheal tone.

These findings suggest that solitary NEE cells in the tracheal epithelium (as NEB in intrapulmonary airways) detect hypoxia via an H₂O₂-producing NADPH oxidase and a closely associated H₂O₂-activated K⁺ channel (4, 15–17). Thus it is postulated that powerful relaxing and contracting factors released from NEE cells in response to different O₂ concentrations modulate the responsiveness of the adjacent airway smooth muscle cells, which, in turn, control the spontaneous tone of the trachea. Interestingly, earlier studies have also shown that lowering the Po₂ induces epithelium-dependent relaxation of canine bronchi (5).

The significance and implications of the study by Skogvall et al. (9) impact on several aspects of postulated PNEC function(s) in normal and diseased lungs. The expression of an O₂-sensing mechanism shared by both solitary PNEC and NEB could form a basis for a unifying hypothesis subject to further studies. A natural stimulus (e.g., O₂ concentration) transduced via an O₂ sensor on PNEC could modulate various pulmonary homeostatic processes, including the airway tone, pulmonary circulation, control of breathing, as well as lung growth and differentiation. Furthermore, the loss or dysfunction of the airway epithelium is a common feature of respiratory diseases characterized by increased airway responsiveness, e.g., asthma and bronchopulmonary dysplasia. It is of interest to note that hyperplasia of PNEC has been reported in both conditions (2). It can also be postulated that airway inflammation via local production of O₂-reactive intermediates, cytokines, and related substances could interfere with the O₂ sensor and thus affect airway responsiveness. Therefore, PNEC could be potential targets for novel therapies. Finally, this neglected cell type has come of age and can now resume its rightful place among other lung cells important in pulmonary function in health and disease.

Address for reprint requests and other correspondence: E. Cutz, Dept. of Pathology, Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8 (E-mail: ernest.cutz@sickkids.on.ca).

REFERENCES