Cough Sensors. IV. Nicotinic Membrane Receptors on Cough Sensors

L.-Y. Lee(✉) and Q. Gu

Contents

1 Cough Evoked by Inhaled Cigarette Smoke ........................................ 78
  1.1 Role of Nicotine in Cigarette Smoke-Induced Airway Irritation .......... 78
  1.2 Cough Receptors in the Lung and Airways ................................. 81
  1.3 Nicotine-Sensitive Afferents in the Lung and Airways .................... 82
2 Neuronal Nicotinic Acetylcholine Receptors on Pulmonary Sensory Neurons ........................................ 85
  2.1 Pharmacological Properties of NnAChRs ...................................... 86
  2.2 Nicotine Sensitivity in Isolated Pulmonary Sensory Neurons .............. 87
  2.3 Expression of NnAChRs on Pulmonary Sensory Neurons .................... 88
3 Other Physiological Functions of NnAChRs on Cough Sensors .................. 90
  3.1 Other Physiological Responses Evoked by Activation of NnAChRs on Pulmonary Afferents ................................. 90
  3.2 Interaction with Other Ion Channels Expressed on Cough Sensors ........ 91
4 Conclusion .................................................................................. 92
References .................................................................................. 94

Abstract Cigarette smoke is undoubtedly one of the most common inhaled irritants in the human respiratory tract, and invariably evokes coughing in both smokers and nonsmokers. Results obtained from the studies in human volunteers and from single-fiber recording of vagal bronchopulmonary afferents in animals clearly indicate that nicotine is primarily responsible for the airway irritation and coughing caused by inhalation of cigarette smoke. Furthermore, both nicotine and acetylcholine can evoke inward current, membrane depolarization, and action potentials in isolated pulmonary sensory neurons, and these responses are blocked by hexamethonium. Taken together, these findings suggest that the tussive effect of nicotine is probably mediated through an activation of nicotinic acetylcholine receptors (nAChRs) expressed on the sensory terminals of cough receptors located in the airway mucosa. Indeed, the expressions of $\alpha_4 - \alpha_7$ and $\beta_2 - \beta_4$ subunits of nAChR transcripts in

L.-Y. Lee
Department of Physiology, University of Kentucky, Lexington, KY 40536-0298, USA
lylee@uky.edu

K.F. Chung, J.G. Widdicombe (eds.), Pharmacology and Therapeutics of Cough, Handbook of Experimental Pharmacology 187,
© Springer-Verlag Berlin Heidelberg 2009
pulmonary sensory neurons have lent further support to this conclusion. The specific subtypes of the neuronal nAChRs and their subunit compositions expressed on the cough sensors remain to be determined.

1 Cough Evoked by Inhaled Cigarette Smoke

One of the most important functions of the cough reflex is to protect the lung and the rest of body from the hazardous effects of inhaled irritants and environmental air pollutants. There is a long list of common inhaled irritants known to elicit cough reflex in humans, including tobacco smoke, dust, automobile exhausts, acid aerosols, noxious gases, allergens, and a variety of airborne chemical irritants. These irritant substances can activate cough sensors either by directly acting on certain ion channels or receptor proteins expressed on the membrane of sensory terminals or indirectly via an action on other target cells in the airways (e.g., bronchial smooth muscles, immune cells such as macrophages or mast cells, etc.) which can in turn evoke stimulatory effects on the cough sensors. Among these tussive substances, cigarette smoke is undoubtedly one of the most common inhaled irritants in human airways.

In nonsmokers, inhaling only a small puff of cigarette smoke can evoke vigorous cough responses and airway irritation. Similar irritant effects can also be generated by brief exposure to the side-stream smoke, the smoke released from a smoldering cigarette (Tarlo 2006). In smokers, cigarette smoking is the major cause of chronic cough (Braman 2006). Indeed, cough not only serves as an important defense function, but is also a common symptom of various airway diseases associated with chronic smoking (Braman 2006); in conjunction with the mucociliary system, cough can expel from the respiratory tract the cigarette smoke constituents that are deposited in the airway lumen as well as the excessive airway secretion produced by smoke inhalation.

1.1 Role of Nicotine in Cigarette Smoke-Induced Airway Irritation

Despite the well-documented irritant effects of inhaled cigarette smoke, the underlying mechanism and smoke constituent(s) that are responsible for generating the airway irritation and cough were not fully understood. In addition to cough, inhaled cigarette smoke can also elicit reflex bronchoconstriction. For a long time, it was suggested that particulates in the cigarette smoke were primarily responsible for the irritant effects and for eliciting reflex bronchoconstriction (Nadel and Comroe 1961). This notion appeared to be consistent with the finding that the irritant receptors in the lung could be activated not only by cigarette smoke but also by “inert” carbon dust (Sellick and Widdicombe 1971). On the other hand, nicotine, a major constituent of cigarette smoke, was known to activate sensory