Controlling from within: neurophysiological plasticity of parasympathetic airway neurons

Richard D. Dey

Department of Neurobiology and Anatomy, West Virginia University, Morgantown, West Virginia 26506

AIRWAY SMOOTH MUSCLE TONE, mucus gland secretion, and blood flow are controlled predominantly by neurotransmitters released from sensory, sympathetic, and parasympathetic neurons with axons that supply the airways (1). The release of neurotransmitters from nerve endings depends on action potentials arriving at the nerve terminals, allowing the influx of calcium through voltage-gated channels (14). Thus the electrical properties of neurons that influence depolarization and subsequent action potential generation are important in determining the release of neurotransmitters from nerve terminals and, consequently, airway reactivity, mucous secretion, and vascular dynamics. Neurotransmitters are released during basal conditions to maintain normal airway function. The parasympathetic neurons of airway ganglia receive presynaptic input originating from preganglionic neurons located in the vagal nuclei of the brain stem (9). Previous studies have shown that <50% of preganglionic impulses reaching the airway ganglia result in the generation of an action potential in the postganglionic neurons (13). Thus neurotransmission through airway ganglia is an important mechanism for controlling neural activity and airway function. Transmission of neural activity through airway ganglia is partially controlled by the intrinsic properties of the airway neurons, notably the excitability of the postganglionic airway neuron. During airway irritation and injury, such as antigen challenge or irritant exposure, newly generated inflammatory mediators are released and may modulate neural activity at synapses in airway ganglia as well as neurotransmitter expression, resulting in altered airway responses having beneficial or detrimental effects on airway function.

Neuronal plasticity is the term used to describe changes in functional and phenotypic properties of neurons. Neuronal plasticity occurring in the airways is a relatively recent discovery but is likely to be an important component of adaptation and defense by the airways and may contribute to airway diseases and conditions such as asthma, bronchitis, chronic obstructive pulmonary disease, and chronic cough. Several mechanisms of plasticity have been identified in airway neurons. In sensory nerves, tachykinin levels are increased by controlling mRNA levels and translation of message to neuropeptide in the nerve cell body. This process provides greater amounts of neuropeptide delivered for delivery to and release from the nerve terminal at the airway target and possibly in the central nervous system. The upregulation of mRNA levels is initiated through neurotrophic molecules like nerve growth factor produced by inflammatory or airway mucosal cells and then transported in axons to the nerve cell body to initiate signaling cascades. There are now several studies describing elevated neurotransmitter levels in sensory neurons of the airways (5, 7, 8). Another example of plasticity in sensory neurons relates to changes in the excitability. Kwong and Lee (10) have recently demonstrated that prostaglandins alter the sensitivity of pulmonary C fibers to mediators like bradykinin and histamine, suggesting that inflammatory mediators may influence electrical activity. Plasticity in postganglionic, parasympathetic-like neurons of airway ganglia has not been studied as extensively as sensory airway neurons, but a few studies suggest that plasticity in these neurons occurs. IL-1 treatment induced substance P (SP) expression in ferret tracheal neurons that normally do not express this neuropeptide (16). These findings support the concept that inflammatory mediators mediate the inflammatory response in the airways. Another example of plasticity in airway parasympathetic neurons is altered neuronal excitability. Neurophysiological studies have demonstrated that antigen challenge increases the excitability of airway neurons and the efficacy of synaptic transmission in airway ganglia (15). The increased firing rate by these neurons enhances neurotransmitter release, predominantly cholinergic, which presumably increases smooth muscle tone, mucous secretion, and general vagal tone in the airways.

The article in focus by Kajekar and coworkers (Ref. 8a, see p. L581 in this issue) confirms and extends previous reports of the excitatory influence of antigen on airway neurons and identifies cyclooxygenase (COX) products as mediators of altered neuronal excitability. Their study shows that airways isolated from guinea pigs passively sensitized and challenged with ovalbumin (OVA) produced large quantities of COX-derived prostanoids, especially PGD2 and thromboxanes. More importantly, they showed that indomethacin or piroxicam, two different COX inhibitors, inhibited accommodation, the ability of some airway neurons to filter preganglionic signals. These findings were confirmed by demonstrating that treatment of airway neurons with PGD2 caused a substantial attenuation of accommodation, and both PGD2 and PGE2 decreased the afterhyperpolarization. The attenuation of accommodation...
tion and the decrease in afterhyperpolarization duration represent electrophysiological changes in active membrane properties that favor increased action potential propagation in the airway neurons. Thus the released prostaglandins promote less accommodation by neurons in airway ganglia, which may lead to enhanced airway vagal tone. Interestingly, the OVA-induced, COX-inhibitable increase in the amplitude of fast excitatory postsynaptic potential (fEPSP) was enhanced by a different prostaglandin, PGF2α, although this prostaglandin was not elevated after OVA exposure. Other prostaglandins tested were without effect on accommodation, afterhyperpolarization duration, or fEPSP. Prostaglandins have been associated with enhancing sensitivity and excitability of pulmonary sensory C fibers (10).

The significance of these studies is that filtering of synaptic signals at the level of postganglionic airway neurons occurs not only during basal conditions but that it is regulated, in this case, attenuated, during immunological challenges through the actions of specific inflammation mediators. One of the important unanswered questions in understanding neural control in airway ganglia relates to how these changes in membrane properties are produced. The active electrophysiological properties of nerve cell membranes that control accommodation, afterhyperpolarization, and fEPSP, are determined predominantly by voltage or ion-coupled sodium and potassium channels. The findings of the current study suggest that ion channels are regulated by mediators generated during inflammation, but identifying the channels involved and determining the influence of inflammatory mediators will require further studies. Another aspect of airway neural control that is not well understood relates to the complex organization of the airway plexus. Although it is tempting to draw a direct correlation between reduced filtering and increased cholinergic tone in airway smooth muscle, the precise phenotypes affected by altered neuronal excitability are not established. For instance, airway neurons are heterogeneous with respect to neurotransmitter phenotype, including the expression of ACh, vasoactive intestinal peptide (VIP), SP, and nitric oxide (NO) (2). Although the neurochemical phenotype of phasic airway neurons (the ones that demonstrate accommodation) in guinea pig airways is cholinergic, the possibility that phasic neurons may also include other neurotransmitter phenotypes warrants additional studies, especially where other phenotypes have been identified, such as in ferrets (2) and in human airways (3). In addition to the cholinergic system, the inhibitory nonadrenergic, noncholinergic (iNANC) system is also represented in neurons of airway ganglia. It is reasonably well established that mediators released from iNANC neurons control smooth muscle relaxation. NO and VIP, both potent relaxant mediators released from airway nerve terminals, are putative transmitters of the iNANC system (4, 6). During airway inflammation, enhanced release of VIP or NO would presumably promote relaxation and might serve to balance increased vagal cholinergic tone. On the other hand, failure of iNANC neurons to respond to inflammatory mediators could mean that only cholinergic neurons are activated, leading to a selective increase in cholinergic influence on airway smooth muscle. Thus it will be important to determine whether all airway neurons are equally responsive to inflammatory mediators or whether subtypes of parasympathetic airway neurons respond differently or are without response. Another consideration that might influence the effect of altered neuronal excitability is connectivity. Complex communications between individual airway neurons are well documented (12, 17), and different circuits may be involved in generating separate local airway reflexes (11). Thus altered neuronal excitability may affect overall activation of the local circuits within the pulmonary plexus.

A role of the airway parasympathetic nervous system in airway dysfunction is slowly emerging. A finding from the current article in focus by Kajekar and coworkers (8a) highlights the importance of airway inflammation and inflammatory mediators in regulating neural activity in the airways and illustrates the range of adaptive mechanisms that may contribute to airway function in health and disease.

REFERENCES
11. Mazzone SB and Canning BJ. Evidence for differential reflex regulation of cholinergic and noncholinergic parasympathetic


