CHAPTER 11
Endothelin-induced Neuromodulation

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1. Introduction

Despite the relative paucity of information with regard to the effects of endothelin on neurotransmission, there are indications that this peptide has functions and effects that extend beyond that of a potent contractor of smooth muscle, and may include that of a neuroactive mediator. Binding sites for endothelin have been found on neural structures, immunoreactive endothelin has been demonstrated within nerves, and endothelin has been shown to have effects on neural functioning, leading to the proposal that endothelin may be a neuropeptide or, alternatively, may be a modulator of neural function [1, 2].

Endothelin is released locally within airways [3, 4], and it is therefore possible that endothelin may have significant effects on neural structures within the lung. Endothelin-like immunoreactivity has been detected in the lung as well as in the associated autonomic nervous supply, in particular, the vagus nerve [5]. Binding sites for endothelin have been localized over nerves in airway connective tissue [6] and a number of studies have recently demonstrated the effect of the endothelin isopeptides on neural activity within the lung. In this chapter, these studies and others will be examined and the suggestion that endothelin is a significant neuromodulator within the respiratory system will be addressed.
2. Endothelin as a Neurotransmitter

The notion that endothelin may be associated with neuronal function was first suggested at the William Harvey Workshop on Endothelin in London in 1989 [1]. Early studies indicated that endothelin-3, may in fact, be a neural form of the peptide [7]. An endothelin-3-like immunoreactive material was shown to be present in porcine brain homogenates and studies of cDNA libraries demonstrated endothelin-3 expression in the human hypothalamus [8]. The detection of endothelin-1-like immunoreactivity in motor neurons and sensory neurons in the spinal cord, and mRNA for endothelin-1 in the human spinal cord and brain [2, 9] suggested that not only endothelin-3, but all members of the endothelin family may be neurotransmitters.

There is, at present, no study in which endothelin has been shown to be released within the lung in response to nerve stimulation induced by application of an electrical field. Significant release of endothelin in response to high frequency electrical stimulation has however been demonstrated in rat iris sphincter. As this release was abolished by tetrodotoxin, this was interpreted as being due to the neural release of the peptide [10]. In addition, endothelin is secreted by hypothalamic neurons in culture [11]. It is therefore not possible to eliminate a neurotransmitter role for endothelin within the peripheral nervous system, but it is more likely that endothelin released from other sites within the lung acts as a local modulator of peripheral nervous function.

3. Endothelin as a Neuromodulator

While there is no evidence to date that the endothelins act as neurotransmitters in the lung, there is evidence that endothelin may amplify or dampen neuronal activity, or the effect of neural activation, therefore satisfying the characteristics required for classification as a neuromodulator. The proximity of the sites of synthesis and release of the endothelin isopeptides to neural structures both in the central and peripheral nervous systems, suggest that the endothelins may influence functioning within these structures. The brain is a richly vascularised structure and endothelin released from vascular endothelial cells may reach sufficiently high local concentrations to alter central neurotransmission. In the lung, transmission through nerve fibres and ganglia may be influenced by endothelin released from epithelial and endothelial cells. Neuromodulators, which do not function as a neurotransmitters, may alter the synthesis, release, interactions with receptors, uptake and metabolism of neurotransmitters, and the results of studies with the endothelins suggest that they fulfil this function.