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EDITORIAL

Neural "crosstalk" in guinea-pig airways - implications for human disease?

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The manuscript in this issue by LINDEN *et al* [1] describes non adrenergic, non cholinergic (NANC) neural responses in guinea pig airways. These authors hypothesise that, when tone is high in the airways, stimulation of these NANC nerves will result in a decrease in tone *i.e.* relaxation of airway smooth muscle, and conversely, in the presence of decreased tone, stimulation will result in a return to an "equilibrium" degree of airway tone.

This is an interesting concept, but it also serves to highlight the lack of corresponding knowledge of the NANC system in human airways. What is known, with a reasonable degree of assurance, of the innervation of human airways, is that there is a parasympathetic excitatory system, contained in the vagus nerves, stimulation of which results in a cholinergically mediated contractile response [2]. There is no evidence for sympathetic innervation directly to the smooth muscle [3] in spite of the presence of a considerable population of beta adrenoceptors in the airways including the airway smooth muscle. Stimulation of these receptors results in relaxation of bronchial smooth muscle *in vitro* [4] and bronchodilation *in vivo*. The absence of direct sympathetic innervation does not, however, rule out the possibility of some degree of "crosstalk" between sympathetic nerve fibres which may innervate the airway vasculature [5] and a neural system, like the parasympathetic, which terminates on the airway smooth muscle.

Evidence for the existence of an atropine-insensitive, *i.e.* non cholinergic, contractile response in human airways *in vitro* is sparse. LUNDBERG *et al.* [6] provided some of the first reports suggesting the presence of a non cholinergic contractile component of the response to electrical stimulation in human bronchus, but others have found this difficult to demonstrate. The most likely candidate as the neurotransmitter for this excitatory NANC system (e-NANC) is one of the tachykinins. Since contraction of human bronchus to exogenous tachykinins is mediated *via* an NK2 receptor [7], this could be neurokinin A or its terminally extended analogue, NPγ [8]. Until recently, it has been difficult to ascribe a role to tachykinins in neurally mediated responses in human airways, as suitable pharmacological antagonists were not available. However, newer specific NK2 antagonists such as SR48968 [9] and NK1 antagonists like CP96345 [10] should enable clarification of this issue.

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The inhibitory NANC response *i.e.* a relaxation of airway smooth muscle observed in the presence of atropine, has been until recently attributed to vasoactive intestinal polypeptide (VIP). However, except in one instance [11], exogenous VIP has proved to be a disappointing relaxant of airway smooth muscle *in vitro* and a poor bronchodilator *in vivo*. BELVISI *et. al.* [12, 13] have, moreover, recently provided some initial evidence for a role for nitric oxide as the inhibitory neurotransmitter in human airways and further studies of this nature should prove invaluable.

As already stated, little is known of the nature of the neurotransmitters of the NANC system in human airways, but even less is known of their modulation in diseases such as asthma. As cited by LINDEN *et. al.* [1] substance P immunoreactive nerves have been reported to be increased [14] and VIP immunoreactive nerves to be decreased [15] in asthmatic lung tissue. However, this has not been corroborated by a corresponding decrease in VIP receptor number [16] nor is there a decrease in expression of VIP receptors in asthmatic lung as measured by mRNA levels [17]. The significance of these findings is questionable in the light of the evidence for NO and not VIP as the inhibitory neurotransmitter. In addition, in human airways, since it is more likely that NKA, rather than substance P would be the endogenous e-NANC neurotransmitter, an increase in substance P immunoreactive nerves may not be pivotal to the elucidation of the primary defect in asthma.

Thus, before we are in a position to postulate on the likelihood of an imbalance in the inhibitory NANC (i-NANC) and e-NANC system contributing to human airway disease, we have to firmly establish the existence of, and the nature of the neurotransmitter in these systems in human, as opposed to guinea pig, or other animal lung.

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