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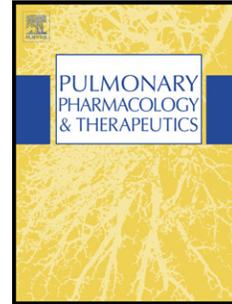
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BASIC POSTER DISCUSSION: SUMMARY**John Widdicombe***

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Keywords: cough; expiration reflex; aspiration reflex; diving reflex; swallow; brainstem; membrane receptors.

Twelve posters were presented in the section on Basic Research. They were discussed in a session chaired by Paul Davenport (Gainesville, US) and Marian Kollarik (Boston, US), with each poster presenter first briefly describing his/her poster.

1. Membrane receptors

Five posters dealt with this topic, of which four were concerned with human cultured cell lines.. One poster (Stokesberry S, Hanrahan S, Polley L, Zholos A, Ennis M, McGarvey L, Functional expression of TRPV1 in primary bronchial epithelial cells) described cultured bronchial cells from chronic coughers and healthy subjects and showed that they expressed TRPV1 receptors and associated protein. Pretreatment with capsaicin induced IL-8 release that was inhibited by capsazepine. The same group (Hanrahan S, Stokesberry S, McGarvey L, Elbon JS, Zholos A, Ennis M. Expression and functional role of TRPM8 in primary human nasal epithelial cells) did similar studies on human nasal epithelial cells (HNECs) in culture. These cells had gene transcripts for TRPM8, and TRPM8 protein was present. Calcium imaging

and patch clamp studies were used to investigate the role of menthol in activating the receptors. *In vivo* the reflex results of activating the bronchial receptors would presumably be cough, and that of the nasal receptors was unknown.

A similar human cloned cell line (HEK293) was used to study the representation of TRPA1 and TRPV1 receptors (Sadofshy LR, Sreekrishna K, Morice AH. Characterization of an HEK293 cell line permanently co-expressing the cough receptors transient receptor potential ankyrin 1 and vanilloid 1 (TRPA1 and TRPV1). Calcium signalling showed that the cells responded to cinnamaldehyde and capsaicin, and that the latter desensitized the response to the former.

These results extended to humans much of the basic research in nonhuman species on membrane receptors involved in cough and other airway reflexes, and provided the molecular basis for understanding cough provocation with capsaicin in humans. This application was illustrated by a further poster (Sreekrishna K, Lin Y, Zhang Y, Eickhoff D, Degenhardt C, Lyon R, et al. Modulation of transient receptor potential (TRP) channels by Chinese herbal extracts). This described the use of the human cloned cell preparation to study four different herbal extracts (used to treat cough) acting on TRP membrane receptors and calcium-flux due to capsaicin. The results are important because they provide a method for testing herbal antitussives on human cells *in vitro*, and because they show that not only may some preparations be effective antitussive agents but that others, inactive in themselves, may potentiate their actions. The results point to potential future antitussive therapies.

The effects of TRPA1 and TRPV1 agonists on capsaicin- and cinnamaldehyde-induced cough in conscious guinea pigs, and on tracheal C-fibres, activity were studied (Brosmanova M, Mazurova L, Ru F, Tatar M, Kollarik M. TPRA1 receptor-mediated cough in the guinea pig). A range of different receptor agonists and antagonists was used, leading to the general conclusion that, for this guinea pig model, TPRA1 receptors are a more powerful activator of cough than are TRPV1 receptors. This linking of membrane receptor activity and afferent 'cough fibre' activity is a valuable approach, and its extension to other receptors (e.g. acid-sensitive, osmosensitive) is highly desirable.

2. Cough motor patterns and interactions

Five posters considered the motor patterns of response of the cough reflex, the expiration reflex and swallow, and of the interaction between these reflexes and between them and the pattern of breathing.

One poster (Pitts T, Rose M, Poliacek I, Sapienza C, Davenport P, Bolser D. Activity patterns of the thyropharyngeus (ThPh) muscle during eupnoea, cough and swallow) introduced swallow as a reflex that would be expected to interact with the pattern of breathing and the cough reflex. This interaction is essential for adequate airway protection. In cats, thyropharyngeus (ThPh) EMG activity was taken as an index of swallow, and its response compared with those of other respiratory muscles. Coughing was induced by mechanical stimulation of the trachea, and swallow by a water bolus in the pharynx. During tracheal stimulation the ThPh EMG was inhibited, but during repetitive coughing the ThPh response to swallow was unchanged. The

interaction of cough and swallow is an important and rather new subject for research, and clearly very relevant to changes after conditions such as stroke where cough-on-swallow is a crucial mechanism, changes in which may lead to aspiration and pneumonia.

The reflex interaction between the CR and nasal stimulation has been much studied recently, the latter potentiating the CR. A poster (Plevkova J, Poliacek I, Adamkov M, Svirlochova K, Jakus J, Tatar M. Expiration reflex from the vocal folds in guinea pigs with experimental allergic rhinitis) applied this approach to the laryngeal ER in the guinea pig. Animals with allergic rhinitis due to ovalbumin were compared with controls and those with intranasal capsaicin. Both allergic rhinitis and capsaicin enhanced the force of the ER and also the number of ensuing coughs. Thus the ER, like the CR, is upregulated by nasal 'irritant' inputs. The results are relevant to sensitisation of cough in post-nasal drip syndrome, and add to the complexity of brainstem integration of defensive reflexes. A rather similar approach was applied with nasopharyngeal mechanical stimulation in cats (Poliacek I, Jakus J, Simera M, Tomori Z. Mutual interaction of airway reflexes—effects of nasopharyngeal vs tracheobronchial stimulations). This stimulus evokes the aspiration reflex (AR)—repeated strong inspiratory efforts with opening of the glottis. ARs induced during the inspiratory phase of cough enhanced the strength of that phase and the strength and duration of the subsequent expiratory phase. When the AR stimulus was applied during the expiratory phase it inhibited the expiratory effort, with little change in timing. Cough induced after ARs was weaker in strength and duration. Thus, like the ER, the AR interacts with cough, but the effect (unlike that of the ER) is in general

down-regulatory. As with the ER (see later) the response depends on the phase of breathing or coughing at which the stimulus is applied.

The importance of the timing of input in relation to the breathing pattern was illustrated. (Varechova S, Poussel M, Schweitzer C, Demoulin B, Chenuel B, Leblanc A-L, et al. Cough and expiration reflex stimulus--response latencies depend on breathing in the rabbit). Using rabbits, the authors showed that brief mechanical stimulation of the trachea could produce either an ER or a CR, depending of the respiratory phase of the stimulus. Delivered in the inspiratory phase of breathing, the CR was significantly more likely to occur than the ER, and *vice versa* for the expiratory phase. The response latencies were significantly shorter for the ER than for the CR. Thus for the same stimulus, the timing of its entry into the brainstem in relation to breathing pattern influences the type of response. This is an important advance on similar studies, because of the brevity and precision of the tracheal stimulus.

Another airway input has been shown to influence the ER and CR (Poussel M, Varechova S, Chenuel B, Schweitzer C, Beyaert C, Marchal F. Effects of the diving reflex on the ventilation response to tracheal irritation in anaesthetized rabbits). The diving reflex consists of inhibition of breathing and closure of the larynx when cold water is applied to the face or into the nose. Of the many respiratory tract reflexes the diving reflex has been the most neglected! The authors showed that cold distilled water applied into the nose of rabbits significantly inhibited the ER and the CR responses to mechanical stimulation of the trachea in rabbits. This makes teleological sense, because cough or sneeze would be undesirable for animals under water. It also

shows that for the nose, as for the lower airways, some afferent inputs sensitize and others desensitize airway defensive reflexes.

3. Brainstem organization of cough

Two posters dealt with central nervous mechanisms regulating cough. One (Bolser DC, Rose MJ, Pitts TE, Davenport PW, Baekey DM, Segers LS, et al. Neurogenesis of airway protective behaviours in the cat: cough and pharyngeal swallow) described medullary neuronal activity in selective 'behavioural control assemblies' (BCAs) when cough was induced by mechanical stimulation of the trachea, and swallowing by pharyngeal injection of water, in cats. Swallows during repetitive cough were restricted to the quiescent period between expiratory efforts (cough E2 phase). The swallow was accompanied by apnoea and increases or decreases in activity of various brainstem neurones in the BCAs. Some neural elements seemed to be common to both cough and swallow BCAs. The same group (Rose MJ, Pitts TE, Poliacsek I, Davenport PW, Morris KF, Bolser DC. Cough-modulated neurone activity patterns in the caudal medial medulla) were recorded from multiple electrode arrays in the cat brainstem, and cough and swallow induced as described above. Some neurones responded similarly to both stimuli, and others showed different patterns of activity. This technically difficult research points to the complexity of the brainstem neuronal networks controlling cough, and how that

complexity is compounded when many inputs are shown to act on the same (and other?) neurones.

Some of us are old enough to remember what used to be called the ‘cough center’. Now we have behavioural control centres that have joint membership and talk to each other, hopefully in the same language. To the non-specialist it may seem that there are too many cough stimulants chasing too many membrane receptors, chasing too many afferent nerve fibres, chasing too many brainstem neurones, chasing too many BCAs, chasing too many patterns of cough and in too many species. Excellent posters such as those described above point towards the complexity of these ‘cough’ mechanisms, and should also lead to a desirable clarification of them.