Activation of ERK1/2 in the caudal nucleus tractus solitarii is required for the mediation of cough reflex responses in the rabbit

Mutolo D.[1], Bongianni F.[1], Cinelli E.[1], Giovannini M.G.[2] & Pantaleo T.[1]

[1]Dipartimento di Scienze Fisiologiche, Viale G.B. Morgagni 63 and [2]Dipartimento di Farmacologia Preclinica e Clinica, Viale Pieraccini, 6, Università degli Studi di Firenze, 50134 Firenze, Italy.

The caudal nucleus tractus solitarii (cNTS) is the first relay medullary station of cough-related afferents. It has been shown to be a site of action of some centrally acting antitussive agents (Mutolo et al, *Am J Physiol Regul Integr Comp Physiol* 2008; 295: R243-R251). A role of Extracellular Signal Regulated Kinases-1 and -2 (ERK1/2) has been suggested in central processing of nociceptive inputs (Obata & Noguchi, *Life Sci* 2004; 74: 2643-2653). Pain and cough share similar features such as the type of afferent fibres (Aδ and C), TRPV1 and TRPA1 membrane receptors as well as central and peripheral sensitization. Thus, an attempt was made to investigate whether ERK1/2 activation could also be involved in the central transduction of tussive inputs. The present research was undertaken on pentobarbitone anesthetized, spontaneously breathing rabbits by using microinjections (30-50 nl) of an inhibitor of ERK1/2 activation (U0126) into the cNTS. Bilateral microinjections of 25 mM U0126 caused rapid and reversible reductions in the cough responses induced by both mechanical and chemical (citric acid) stimulation of the tracheobronchial tree. The cough number and peak abdominal activity decreased. Bilateral microinjections of 50 mM U0126 completely suppressed the cough reflex without affecting the Breuer-Hering inflation reflex, the pulmonary chemoreflex and the sneeze reflex. These U0126-induced effects were, to a large extent, reversible. Bilateral microinjections of the inactive analogue of U0126 (50 mM U0124) at the same cNTS sites did not cause appreciable effects. This is the first study that provides evidence that ERK1/2 activation within the cNTS is required for the mediation of cough reflex responses in the anesthetized rabbit. These results suggest a role for ERK1/2 pathway in the processing of tussive inputs by nontranscriptional mechanisms, given the short time lapsed from ERK1/2 inhibition and cough response suppression. Interestingly, studies on the involvement of MAPK pathways in central and peripheral transduction mechanisms of tussive stimuli may provide fruitful strategies for the development of novel antitussive therapies.

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