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Title: Bidirectional modulation of urge to cough by nasal TRPA1 and TRPM8 agonists in healthy human subjects

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Body: Cough, the most important airways defensive mechanism is modulated by many afferent inputs either from respiratory tussigenic areas, but also by afferent drive from other organs. Modulation of cough by nasal afferent inputs could either facilitate cough response or inhibit it in animal models, depending on the type of trigeminal afferents which are stimulated. In recent study we addressed the question of possible bidirectional modulation of cough response in human healthy volunteers by nasal challenges with TRPA1 and TRPM8 agonists respectively. After nasal challenges with AITC, cinnamaldehe, (-) menthol and (+) menthol (all 10-3 M, nasal symptom score, cough threshold (C2), urge to cough (Cu) and cumulative cough response had been tested). Nasal challenges of TRPA1 relevant agonists induced considerable nasal symptoms, significantly enhanced urge to cough ($p < 0.05$) but modulation of C2 and cumulative cough response did not reach significance level. Both TRPM8 agonists administered to the nose significantly modulated all parameters including C2 (p0.05), Cu ($p< 0.01$) and cumulative cough response ($p < 0.001$) documenting strong anti irritating potential of menthol isomers. Except the role of trigeminal afferents expressing TRP channels, also olfactory nerve endings, trigemino – olfactoric relationships, smell perception process and other supramedullar influences have to be taken into consideration as relevant enough to modulate cough response in humans. supported by VEGA 1/0031/11.