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Title: Urge to cough is significantly abolished by nasal thymol application

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Body: Thymol is empirically used to relieve symptoms of respiratory diseases. It is a component of thyme herb extract, a terpene with antibacterial, antifungal, and antioxidative activity. In the respiratory system it is known to modulate mucociliary transport, airway β_2 receptors, and combined with ivy extract attenuates coughing in children with acute bronchitis. Thymol also acts on the transient receptor potential cation channel, subfamily V, member 3 (TRPV3) channels which are expressed in the skin, tongue, and afferent somatosensory neurons. In the present study we tested hypothesis that intranasal administration of thymol would modulate the cough reflex possibly by trigeminal/olfactory pathways. Eighteen healthy volunteers with normal lung function were tested for cough. Before and after nasal administration of thymol (0.025 ml, 10⁻³M) into both nostrils, urge-to-cough, cough threshold, cumulative and total count of coughs per provocation were estimated during standardized and validated capsaicin cough challenge. Nasal thymol challenges induced pleasant olfactory sensations and in 6 out of the 18 subjects also a transient (up to 2 min) mild cooling sensation. Cough threshold was not influenced when compared with intranasal saline and vehicle challenges (12.5 vs. 13.2 vs. 10.2 μ M of capsaicin to induce two or more coughs (C2), respectively, but the total count of coughs after nasal thymol challenge was significantly lower than that obtained after saline or vehicle (19 vs. 20 vs. 14 coughs/provocation, respectively; p<0.05). Importantly, subjects did not report the urge to cough, which appeared to correspond to C2. We conclude that the modulation of cough by thymol is, to a great extent, of olfactory origin.