The Respiratory Response of TRPV1 Knockout Mice to Trigeminal Irritants

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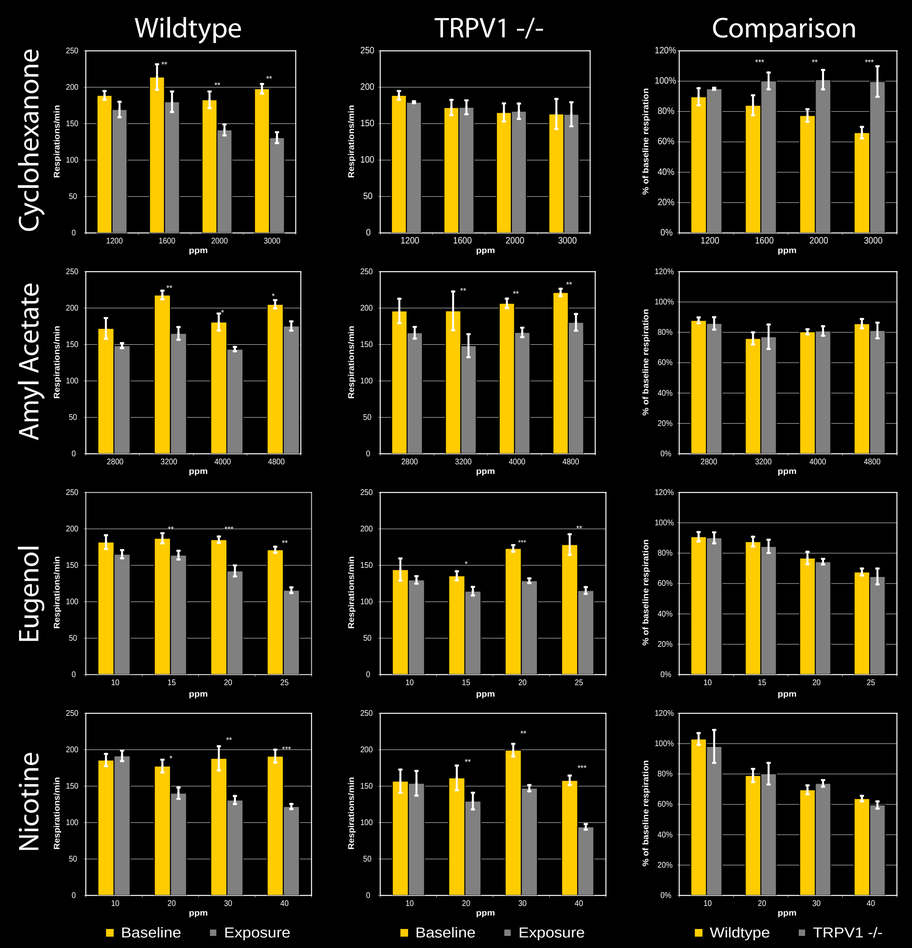
Introduction

The trigeminal nerve is composed of polymodal neurons which innervate the nasal cavity, nasopharynx, oral cavity and cornea.[4] Although trigeminal nociceptive fibers are stimulated by a wide variety of chemical irritants, the mechanism of stimulation is known for only a few compounds. TRPV1 channels, for example, are activated by capsaicin.[5] The objective of this study is to determine if TRPV1 is required for the detection of four known trigeminal irritants: cyclohexanone, amyl acetate, eugenol and nicotine.

Methods

Classic studies using the "Alarie Test" have established that upper respiratory tract irritants cause a systematic alteration in normal exhalation pattern which results in a decreased respiration rate (Fig 1).[2,7] In the present study, an air dilution olfactometer (Fig 2) was used to administer volatile compounds to unanesthetized mice in a double chambered plethysmograph. Respiration rate depression for female wildtype (C57Bl/6J) mice was calculated with AcqKnowledge (BIOPAC Systems Inc, Goleta, CA) and compared to female TRPV1 knockout mice for a variety of compounds in an attempt to determine if TRPV1 was responsible for the detection of these irritants. Baseline respiration was recorded for 5 min. Respiration was then recorded for 5 min during irritant exposure. 16 wildtype mice were sampled once per chemical, in groups of four. 12 TRPV1-/- mice were tested in groups of four; one group was exposed twice to each chemical. Groups of mice were assigned to a concentration randomly. During 3 day breaks between exposures, mice were housed in groups of 4, allowed food and water *ad libitum* and were maintained on a 12 hour light cycle. All mice were purchased from Jackson Labs (Bar Harbor, ME)

Results



Each bar represents mean ± SEM of four mice. * p<0.05 ** p<0.01 ***p<0.001 by paired one-tailed T-test

Methods (continued)

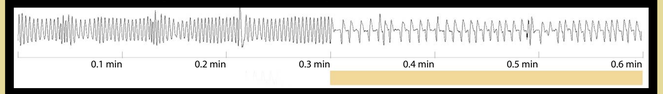


Figure 1. Sample trace from a wildtype mouse in a double chamber plethysmograph. Bar marks exposure to 3000 ppm cyclohexanone.

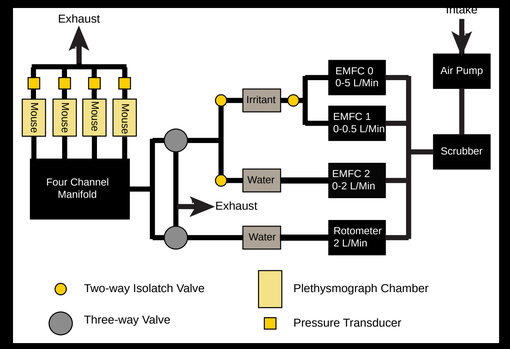


Figure 2. Diagram of the computer-controlled air dilution olfactometer constructed for these experiments.

Discussion

TRPV1 knockout mice did not show significant respiratory rate depression when exposed to cyclohexanone, a known TRPV1 agonist.[6] Amyl acetate, eugenol and nicotine caused a significant respiratory rate depression in wild type and TRPV1-/- mice. It appears that cyclohexanone is primarily detected by TRPV1, while the detection of amyl acetate, eugenol and nicotine are mediated by other receptors. Eugenol and nicotine are most likely being detected by TRPA1[3] or TRPV3[8] and nAChR[1], respectively.

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