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Neural Correlates of Oral Irritation by Mustard Oil and other Pungent Chemicals: A Hot Topic

E. Carstens and T. Mitsuyo

Section of Neurobiology, Physiology and Behavior, University of California, Davis, 1 Shields Avenue, Davis, CA 95616, USA

Correspondence to: E. Carstens, e-mail: eecarstens@ucdavis.edu

Together with taste and smell, oral sensations of touch, temperature, chemical irritation and pain play an important role in determining food flavor. Trigeminal sensations are mediated by sensory fibers innervating the oral mucosa that project via the lingual nerve to reach the brainstem trigeminal complex, with extensive terminations in subnucleus caudalis (Vc) (Carstens *et al.*, 1995). Neurons in superficial laminae of dorsomedial Vc often respond to a wide range of thermal, mechanical and irritant chemical stimuli (Carstens *et al.*, 1998).

Different pungent chemicals elicit distinct temporal patterns of oral irritation. Repetitive application of capsaicin elicits a progressive rise in irritancy (sensitization; Green, 1989), as do piperine and concentrated salts and acids. In contrast, nicotine, menthol and cinnamaldehyde elicit irritation that declines across trials (desensitization; for a review, see Carstens *et al.*, 2002). These contrasting patterns are also observed in the responses of Vc neurons (Dessirier *et al.*, 2000) and may depend on the relative strength of opposing excitatory and desensitizing processes that are initiated in trigeminal nerve endings by a particular irritant.

Recent molecular studies have uncovered the existence of six transient receptor potential (TRP) channels that account for thermal sensations from extreme cold to extreme heat (Jordt *et al.*, 2003; Montell, 2003). Several of these also respond to irritant chemicals. Thus, TRPV1 (VR-1) is activated by noxious heat and capsaicin (Caterina *et al.*, 1997), TRPM8 (CMR-1) by cooling and menthol (McKemy *et al.*, 2002; Peier *et al.*, 2002) and TRPA1 (ANKTM1) by intense cold, mustard oil, cinnamaldehyde, cannabinoids and other chemicals (Story *et al.*, 2003; Bandell *et al.*, 2004; Jordt *et al.*, 2004). Our laboratory is particularly interested in the sensory properties of mustard oil in relation to TRPA1.

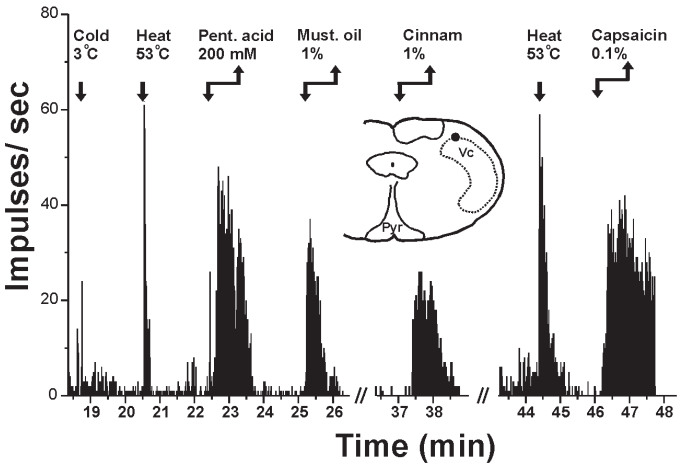

Figure 1 Cold-sensitive Vc neuron. Peristimulus–time histogram (PSTH; bin width 1 s) shows responses to the indicated stimuli applied to the dorsal anterior tongue (downward arrows), recorded in rat anesthetized with 1.2% halothane. For chemical stimuli, the upward arrow shows time of rinse 1 min after stimulus application. Unit was unresponsive to menthol (data not shown). The histologically localized recording site in superficial dorsomedial Vc is shown in the inset. Abbreviations as in the legend to Figure 2B.

In psychophysical experiments, lingual application of mustard oil (allyl isothiocyanate, 0.125%) elicited a desensitizing pattern of oral irritation and exhibited mutual cross-desensitization with capsaicin (Simons *et al.*, 2003). Mustard oil similarly elicited a desensitizing firing pattern in Vc neurons recorded in anesthetized rats and cross-desensitized responses to pentanoic acid (Simons *et al.*, 2004). However, mustard oil (1.25%) sensitized Vc responses to noxious heat, consistent with its well-known sensitizing effect on the skin. These contrasting effects of mustard oil (i.e. heat sensitization and chemical desensitization) are not consistent with peripheral or central sensitization, but might reflect a TRPA1-mediated enhancement of thermal gating of TRPV1 and an inhibition of chemical gating of TRPV1 (or other channels) co-expressed in the same trigeminal nerve endings.

TRPA1 is activated by intense cold, mustard oil and cinnamaldehyde (Bandell *et al.*, 2004) and we routinely record from Vc neurons that respond to these stimuli as well as to noxious heat and capsaicin (but not menthol). An example is shown in Figure 1. TRPA1 exhibits desensitization to repeated cooling (Story *et al.*, 2003). We observed a significant decline in successive responses of Vc neurons to repeated lingual cooling (3°C) at rapid (15 s) intervals (Figure 2A,C). Vc responses usually also exhibited desensitization to repeated application of mustard oil or cinnamaldehyde (Figure 2B). Moreover, cold-evoked responses were significantly reduced following application of mustard oil or cinnamaldehyde (Figure 2B,D), suggesting a TRPA1 chemically mediated cross-desensitization of thermal gating of TRPA1.

In conclusion, a substantial population of Vc neurons receives input from trigeminal afferents expressing TRPA1 and/or TRPV1, with some properties of TRPA1 being reflected in the responses of Vc neurons. It is curious that mustard oil, associated with a burning quality and intense cold, both apparently act via a common transduction mechanism. It is additionally puzzling as to how the nervous system can make qualitative discriminations based on input from neurons that respond to both noxious hot and cold stimuli. Nevertheless, the discovery of thermo- and chemosensitive TRP channels has certainly spiced up the field of trigeminal chemoreception.

Acknowledgements

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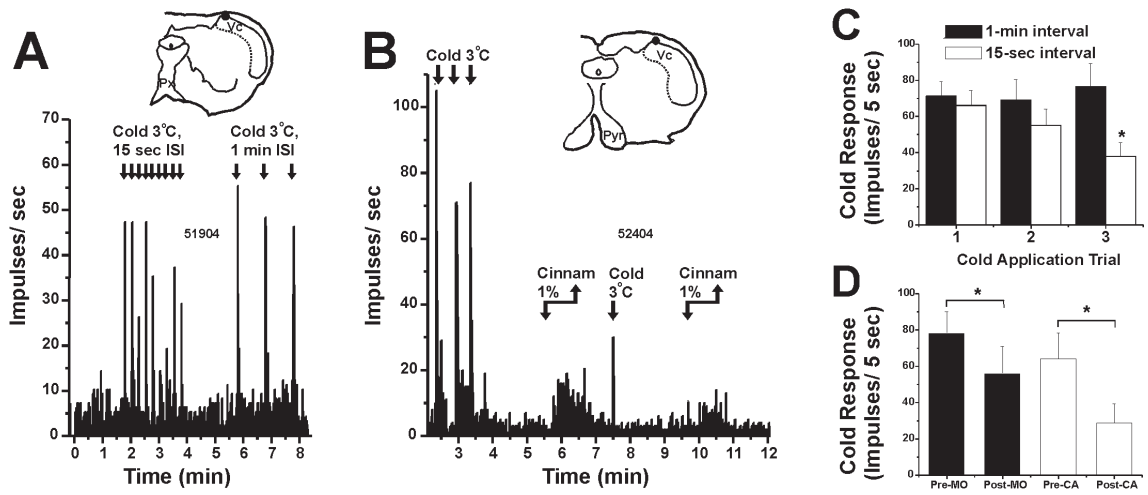

Figure 2 Responses of Vc units to cold stimulation. **(A)** PSTH of Vc unit's responses to repeated brief applications of cold water (arrows; 1 ml/3 s) at interstimulus intervals (ISI) of 15 s (left) and 1 min (right). Note the greater reduction in successive responses at the faster application rate. Upper drawing shows Vc recording site (abbreviations given in B). **(B)** PSTH from a different Vc unit showing responses to cold water (arrows), followed by cinnamaldehyde (downward-upward arrows), with reduced response to cold after that. Note also the reduced response to a second application of cinnamaldehyde. Corresponding recording sites in dorsomedial superficial Vc are shown in upper drawings. Vc, trigeminal subnucleus caudalis; Pyr, medullary pyramid; Px, pyramidal decussation. **(C)** graph plots mean responses of Vc units to cold stimuli (impulses/5 s after stimulus onset) applied at 1 min (black bars) or 15 s intervals (open bars). Error bars indicate SEM. *Significantly less than trial 1 ($P < 0.05$, $n = 10$). **(D)** Mean responses to cold before and after application of 10% mustard oil (MO, black bars) or 1% cinnamaldehyde (CA, open bars). *Significantly different ($P < 0.05$, $n = 10$).

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