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Desflurane induces airway contraction mainly by activating transient receptor potential A1 of sensory C-fibers

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Abstract
We previously reported that desflurane induced airway contraction via antidromic tachykinin release from sensory C-fibers. Here, we investigated the effect of desflurane on airway lung resistance (R_L) using specific receptor antagonists in C-fibers. Young guinea pigs were anesthetized and their tracheas were cannulated with an endotracheal tube via a tracheotomy. A Fleisch pneumotachograph and a differential transducer were used to monitor respiratory flow rate, intrapleural pressure, and airway pressure, and R_L was calculated and recorded. A transient receptor potential A1 (TRPA1) or a transient receptor potential V1 (TRPV1) selective antagonist of sensory C-fibers, i.e., HC030031 or BCTC, was administered before the exposure to desflurane. In an additional experiment, tachykinin receptor of airway smooth muscles was antagonized only by the neurokinin-2 receptor antagonist MEN-10376 before the exposure to desflurane. HC030031 completely inhibited both the first and the second contractile responses induced by desflurane, whereas BCTC had little effect. MEN-10376 also significantly and substantially diminished the contractile response. Desflurane contracts the airway in untreated guinea pigs mainly by activating irritant gas receptor TRPA1 of afferent C-fibers, resulting in the release of contractile tachykinins such as neurokinin A.

Key words Desflurane · Lung resistance · Transient receptor potential A1 · Afferent C-fiber

It is well known that volatile anesthetics such as sevoflurane are potent bronchodilators [1]. The bronchodilation induced by volatile anesthetics occurs indirectly by their inhibition of reflex neural pathways [2] and directly by their effects on airway smooth muscle cells [3]. Although there is evidence that desflurane (as well as other volatile anesthetics) can also directly relax preconstricted airway smooth muscle in vitro [4,5], it increases the airway resistance in patients regardless of the presence of hyperreactive airway disease [6,7]. We recently reported that desflurane, but not sevoflurane, induced airway contraction in untreated guinea pigs via antidromic tachykinin release from afferent C-fibers, but not via acetylcholine release from parasympathetic efferent nerves [8]. However, the precise targets of tachykinin pathways affected by desflurane are still unknown. We therefore investigated the effect of desflurane on airway lung resistance (R_L), using specific receptor antagonists in sensory C-fibers.

The protocol was approved by the Animal Care and Use Committee of our institution. As in our previously reported studies [8,9], young (5-week-old), male, pathogen-free Hartley guinea pigs, weighing approximately 300 g, were used in this study ($n = 6$ in each experiment). The animals were anesthetized intraperitoneally with urethane (1 g·kg^{-1}). The trachea was cannulated with an endotracheal tube (PE-240; Becton Dickinson Diagnostics, Sparks, MD, USA) just below the larynx via a tracheotomy. The animals were ventilated with a respirator (model 683; Harvard, South Natick, MA, USA) at a constant rate of 45 breaths·min^{-1} and a tidal volume of approximately 6–8 ml·kg^{-1}. The intrapleural pressure was measured via a water-filled cannula that was placed in the lower third of the esophagus and connected to one port of a differential pressure transducer. The transpulmonary pressure was determined by monitoring the difference between the pressure in the external end of the tracheal cannula and the pressure in the esophageal cannula, using a Statham differential transducer (DP-45; Validyne Engineering, Northridge, CA, USA). A Fleisch pneumotachograph and a differential transducer were used to monitor respiratory flow rate (PULMOS-II; Medical Interface Project Station, Osaka, Japan) [10]. All signals were recorded and R_L was analyzed continuously by an online computer on a breath-by-breath basis. To observe the effects of desflurane on R_L in guinea pigs, the animals were exposed to the anes-

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thetic (2.0 minimum alveolar concentration [MAC]) for 10 min via tracheotomy with the use of a calibrated vaporizer. The MAC value of desßurane for guinea pigs was established as 6.4% [11]. An irritant gas receptor transient receptor potential A1 (TRPA1) or capsaicin receptor transient receptor potential V1 (TRPV1) selective antagonist of afferent C-Þbers, i.e., HC030031 (3 mgákg^{-1}) [12,13] or BCTC (2 mgákg^{-1}) [14,15] was administered intravenously 15 min before the exposure to 2.0 MAC desßurane. In an additional experiment, tachykinin receptor of airway smooth muscles was antagonized by a tachykinin neurokinin 2 (NK_2) receptor antagonist (i.e., NKA antagonist), MEN-10376 (3 mgákg^{-1}) [16], 15 min before the exposure to 2.0 MAC desßurane. A heating pad was placed under each animal and the rectal temperature was kept at approximately 37¡C during the study period. All data are presented as raw data or means ± SD. The effects of desßurane on measured parameters were analyzed by the unpaired *t*-test. A *P* value of less than 0.05 was considered to be signiÞcant.

As reported previously [8], exposure to a high concentration of desßurane (2.0 MAC = 12.8%) distinctly increased R_L biphasically. The change in the R_L induced by desßurane showed biphasic responses, and thus the data are shown as the changes in the Þrst and second peaks in the summarized Þgures. Figure 1 summarizes the effects of the TRPA1 selective antagonist HC030031 and the TRPV1 selective antagonist BCTC on the desßurane-induced contractile responses. The TRPA1 receptor antagonist HC030031 completely inhibited both the Þrst and the second contractile responses

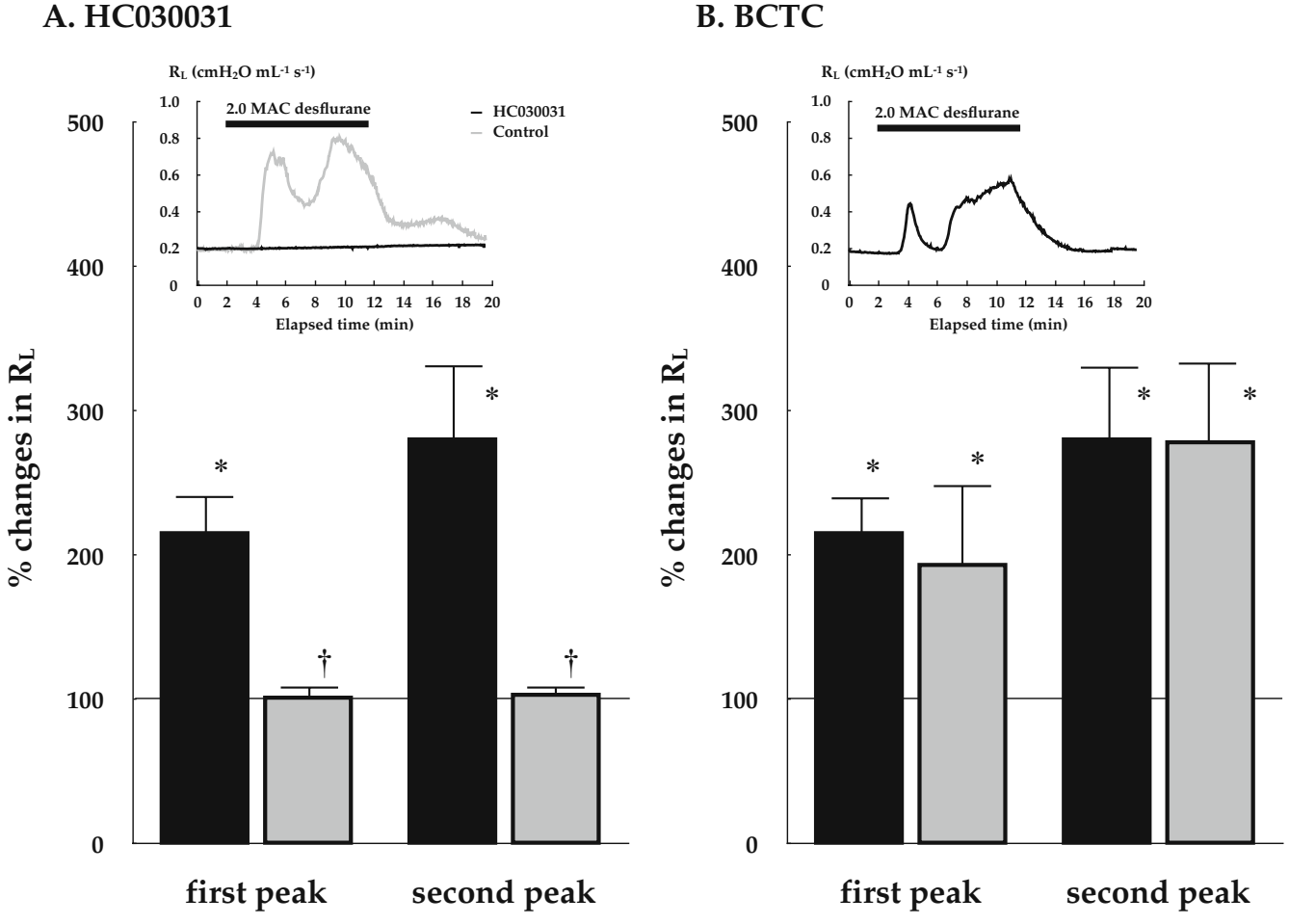

Fig. 1A,B. Effects of 2.0 minimum alveolar concentration (*MAC*) desßurane on percent changes in total lung resistance (R_L) in pretreatment with the transient receptor potential A1 (TRPA1) and TRPV1 selective antagonists HC030031 (3 mgákg^{-1}; *black bars*; **A**) and BCTC (2 mgákg^{-1}; *black bars*; **B**). Raw data for each experiment are shown in the *inset* Þgures. Data are expressed as means ± SD; $n = 6$ each. *$P <$ 0.05 vs baseline without exposure to anesthetic; $P < 0.05$ vs the control values obtained by exposure to desßurane (*white bars*). The TRPA1 selective antagonist HC030031 completely inhibited both the Þrst and the second contractile responses induced by desßurane, whereas the TRPV1 selective antagonist BCTC had little effect on these responses

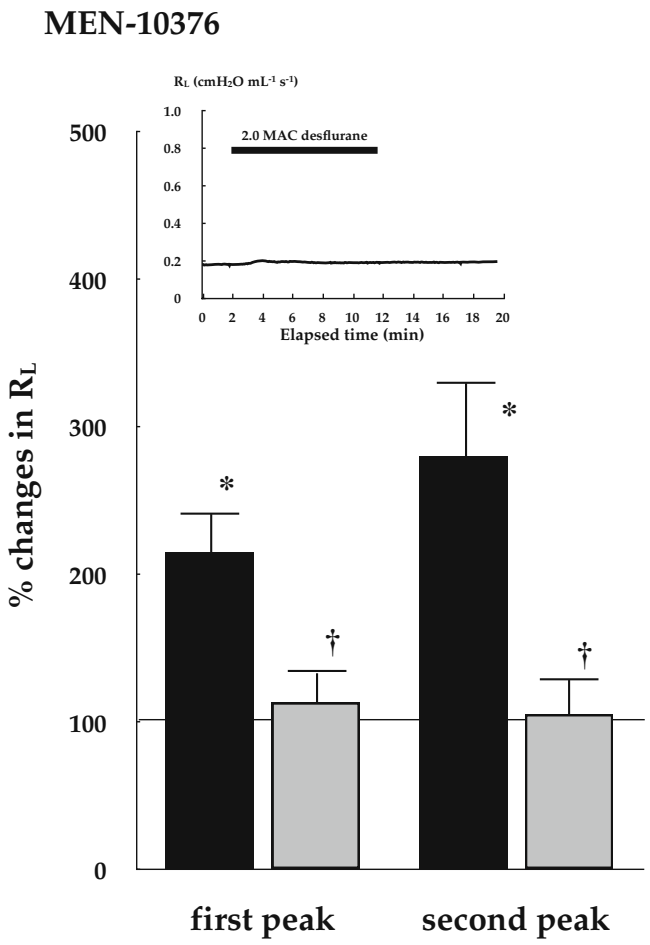

Fig. 2. Effects of 2.0 minimum alveolar concentration (*MAC*) desßurane on percent changes in total lung resistance (R_L) in pretreatment with the tachykinin neurokinin 2 receptor selective antagonist MEN-10376 (3 mgákg^{-1}; *black bars*). Raw data for each experiment are shown in the *inset* Pgure. Data are expressed as means ± SD; $n = 6$ each. *$P < 0.05$ vs baseline without exposure to anesthetic; $P < 0.05$ vs the control values obtained by exposure to desßurane (*white bars*). MEN-10376 signiPcantly and substantially diminished the contractile responses

induced by desßurane, whereas the TRPV1 receptor antagonist BCTC had little effect on them. Figure 2 summarizes the effect of the tachykinin NK_2 receptor selective antagonist MEN-10376 on the desßurane-induced contractile responses. As clearly demonstrated in this Pgure, MEN-10376 signiPcantly and substantially diminished the contractile responses.

This study revealed that the irritant gas receptor TRPA1 of sensory C-Pbers and the tachykinin NK_2 receptor of airway smooth muscle mainly contributed to desßurane-induced airway constriction. This result is consistent with previously reported studies in which volatile anesthetics activated TRPA1 expressed on HEK cells [17] and activated TRPA1 in mice [18]. The TRP channel, TRPA1 (mustard-oil receptor), a nonselective cation channel activated by mustard-oil or irritant gases [19], is co-expressed with TRPV1 in vagal C-Pber neurons in the airway [12,20]. Various receptors such as TRPA1 and TRPV1 are expressed in the airway terminal of sensory C-Pbers [12], and the membrane potential is increased and action potential is triggered by activating any of these receptors, resulting in signal transduction in the C-Pbers and in tachykinin release [17]. Pretreatment with the TRPA1 selective antagonist HC030031 completely diminished the contractile response induced by desßurane, suggesting that this anesthetic could cause airway contraction via this pathway. Because irritant gases such as those in cigarette smoke also activate TRPA1 [21], it seems that desßurane could induce severe bronchoconstriction during general anesthesia.

On the other hand, activation of C-Pbers can release the tachykinins substance P, calcitonin gene-related peptide (CGRP), and neurokinin A (NKA) antidromically. Of these substances, substance P and NKA are two major types of tachykinins identiPed in the mammalian respiratory tract, and these tachykinins are co-localized on C-Pbers in the airway of guinea pigs [22,23]. Especially, NKA released via an axon reßex potently constricts airway smooth muscle in guinea pigs via NK_2-receptors [24]. Pretreatment with the NK_2 receptor selective antagonist MEN-10376 completely diminished the desßurane-induced airway contraction, indicating that NKA released from C-Pber terminals is the main contributor to the desßurane-induced airway contraction.

In our experiments, desßurane increased the airway lung resistance biphasically. Cervin and Lindberg [25] also reported that desßurane increased mucociliary activity biphasically and that pretreatment with a tachykinin antagonist inhibited both responses, but pretreatment with atropine had no effect on the responses. In our experiments, pretreatment with the TRPA1 selective antagonist HC030031 also diminished both responses, and pretreatment with the TRPV1 receptor antagonist BCTC had little effect on them. Although tachykinin pathways may have some role in the effect of desßurane, the implications of the biphasic responses to desßurane are still unknown.

In conclusion, desßurane contracts the airway in untreated guinea pigs by activating the irritant gas receptor transient receptor potential A1 (TRPA1) of afferent C-Pbers, resulting in the release of contractile tachykinins such as NKA.

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