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Effect of olvanil on the afferent and efferent function of capsaicin-sensitive C-fibers in guinea pig airways

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Abstract

The aim of the present study was to examine the ability of the nonpungent vanilloid VR1 receptor agonist, olvanil, to activate the afferent and efferent function of capsaicin-sensitive C-fibers in guinea pig airways. We found that while capsaicin (10 nM–10 μM) and resiniferatoxin (0.1 nM–1.0 μM) evoked a robust contraction of the guinea pig trachea in vitro, olvanil (10 nM–10 μM) was a weak spasmogen. In addition, pretreatment with olvanil caused only a minor reduction of subsequent responses to capsaicin or resiniferatoxin. Using single fiber recording from guinea pig airway C-fibers, we found that olvanil (10 μM) did not evoke action potential discharge although these fibers responded vigorously to capsaicin after prolonged treatment with olvanil (10 μM). These findings are indicative of significant differences in the relative sensitivity of vanilloid VR1 receptor-transfected cells and the peripheral terminals of airway C-fibers to pungent and nonpungent vanilloid VR1 receptor agonists.

Keywords: Vanilliod VR1 receptor; Olvanil; Capsaicin-sensitive C-fiber; Airway C-fiber; Vanilloid

1. Introduction

Capsaicin, a pungent component of chili peppers, selectively activates a subset of nociceptive afferent neurons resulting in the generation of action potentials and release of neuropeptides from their central and peripheral terminals (Szallasi et al., 1999). These effects of capsaicin are mediated by the vanilloid VR1 receptor, a recently cloned nonselective cation channel (Caterina et al., 1997). The initial excitation of sensory nerves by capsaicin is followed by prolonged desensitization of these nerves not only to capsaicin, but also to other noxious stimuli that would normally evoke action potential discharge, including electrical stimulation (Dray et al., 1990; Szolcsanyi, 1977). This effect of capsaicin also appears to be mediated by activation of the vanilloid VR1 receptor followed by inhibition of neuronal voltage-gated Na^+ currents (Liu et al., 2001).

A variety of compounds with agonist activity at the vanilloid VR1 receptor have been described, however, not all vanilloid VR1 receptor agonists are equally effective at evoking action potential discharge, neuropeptide release or desensitization of capsaicin-sensitive neurons. There is a potential clinical benefit of nonpungent vanilloid VR1 receptor agonists that retain their ability to desensitize nociceptors (Szallasi and Blumberg, 1999). The capsaicin analogue olvanil is an example of a nonpungent vanilloid VR1 receptor agonist. Despite being as potent and efficacious as capsaicin at evoking vanilliod VR1 receptor-mediated responses in transfected Human Embryonic Kidney (HEK) 293 cells (Jerman et al., 2000; Smart et al., 2001) or Ca^{2+} uptake in dorsal root ganglion cell bodies (Walpole and Wrigglesworth, 1993), olvanil is far less pungent than capsaicin (Brand et al., 1987). However, both capsaicin and olvanil have been reported to have antinociceptive properties (Brand et al., 1987; Dickenson et al., 1990; Dray and Dickenson, 1991; Hayes et al., 1984).

In the airways, the activation of capsaicin-sensitive C-fibers leads to centrally mediated reflexes such as cough (Lalloo et al., 1995) while the release of tachykinins from their peripheral terminals results in airway smooth muscle contraction (Ellis and Undem, 1994; Maggi et al., 1991) and neurogenic inflammation (McDonald et al., 1988). There is much speculation of a role for sensory nerve-mediated processes in inflammatory airway disease such as asthma

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(Undem and Carr, 2002) and the ability to selectively inhibit the function of these fibers may be clinically beneficial. One possible strategy is the use of a nonpungent vanilloid VR1 receptor agonist such as olvanil, to desensitize C-fibers without first activating them, thus avoiding the unpleasant responses associated with the excitation of C-fibers. However, the action of olvanil on the afferent and efferent function of airway C-fibers is unknown. In this study we have examined that ability of the VR1 agonist olvanil to excite and desensitize the afferent and efferent function of C-fibers in guinea pig airways.

2. Materials and methods

2.1. Tissue preparation

Male Hartley guinea pigs (200–400 g) were euthanized by asphyxiation with CO_2 and exsanguinated following the guidelines of the UCB Research Institutional Animal Care and Use Committee. For contraction studies, the trachea were removed and placed in a dissecting dish containing Krebs bicarbonate buffer solution (KBS) composed of (in mM): NaCl, 118; KCl, 5.4; NaH_2PO_4, 1.0; $MgSO_4$, 0.6; $CaCl_2$, 1.9; $NaHCO_3$, 25.0; dextrose, 11.1. For electrophysiological studies the airways with intact right-side extrinsic innervation (including nodose and jugular ganglia) were removed and placed in a dissecting dish containing KBS.

2.2. Contraction studies

The lower trachea was divided into horizontal strips, each roughly three cartilage rings in width. Tracheal strips were placed in tissue baths then tied with silk surgical suture to force–displacement transducers (FT03C, Grass Instrument, Quincy, MA) for recording of isometric tension on a computerized data acquisition system (EMKA Technologies, Paris, France). Resting tension was set at 1.5*g*. Tissue baths contained 10 ml of KBS, which was maintained at 37 °C and bubbled with 95% O_2–5% CO_2 and replaced every 15 min during a 60 min equilibration period. The cyclooxygenase inhibitor indomethacin (10 μM) was present in the KBS throughout all studies to prevent release of cyclooxygenase products. Following the equilibration period, 3.0 μM histamine was added to the baths for 15 min. Tissues were then washed for 15 min and 3.0 μM histamine was again added to baths for 15 min. Tissues were then washed repeatedly until the recorded tension returned to baseline. Following a 30-min period with washing every 15 min, vanilloid receptor 1 agonist (olvanil, resiniferatoxin or capsaicin) was added to construct concentration response curves. Only one concentration response curve was constructed in each tissue. Vanilloid VR1 receptor agonists were added in a cumulative manner to achieve the desired concentration (0.1 nM–1.0 μM for resiniferatoxin, 10 nM–10 μM for capsaicin and olvanil). 30 mM $BaCl_2$ was added at the end of each experiment to obtain a maximum contraction.

In a separate set of experiments, cross-desensitization was examined using concentrations of vanilloid VR1 receptor agonists selected from the concentration response curves. Trachea were pre-contracted with histamine as described above. After washing the tissues for 30 min, trachea were pre-incubated with a single concentration of vanilloid VR1 receptor agonist (10 μM olvanil, 1.0 μM capsaicin, or 0.1 μM resiniferatoxin) for 30 min. At the end of this period, tissues were washed for 60 min, replacing KBS every 15 min. After the wash period, a vanilloid VR1 agonist different from that used during the pre-incubation period was added to each tissue. After the maximal response was achieved, 30 mM $BaCl_2$ was added to obtain a maximum contraction.

2.3. Electrophysiological studies

Guinea pig isolated trachea/bronchus was prepared, as previously described (Riccio et al., 1996) for the extracellular recording of action potential discharge in jugular afferent nerve fibers that have defined a receptive field in the airways. Briefly, connective tissue was carefully trimmed away from the trachea, larynx and right bronchus leaving the vagus, superior laryngeal, and recurrent nerves, including nodose and jugular ganglia intact. A longitudinal cut was made to open the larynx, trachea and bronchus along the ventral surface. Airways were then pinned, mucosal surface up, to a Sylgard-lined Perspex chamber. The right nodose and jugular ganglia, along with the rostralmost vagus and superior laryngeal nerves, were gently pulled through a small hole into an adjacent compartment of the same chamber for recording of single fiber activity. Both compartments were superfused with KBS gassed with 95% O_2–5% CO_2 The temperature was maintained at 35 °C with a flow rate of $\approx$ 5 ml min^{-1}.

2.4. Extracellular recordings

Fine aluminosilicate glass microelectrodes were pulled using a Flaming/Brown micropipette puller (Sutter Instrument, Novato, CA, USA) and filled with 3 M sodium chloride. The filled electrode was placed into an electrode holder and connected directly to a headstage (A-M Systems, Everett, WA, USA). A return electrode of silver–silver chloride wire and a silver–silver chloride pellet ground were placed in the perfusion fluid of the recording chamber and attached to the headstage. The recorded signal was amplified (A-M Systems) and filtered (low cut-off = 0.3 kHz; high cut-off = 1 kHz) and the resultant activity was displayed on an oscilloscope (TDS 340, Tektronix, Beaverton, OR, USA) and digitized (CED 1401, Cambridge Electronic Design, Cambridge, UK). The data were stored for off-line analysis on a PC computer using the software program Spike 2 for Windows version 4 (Cambridge Electronic Design).

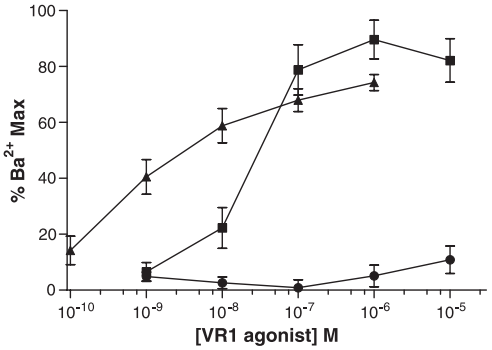

Fig. 1. Cumulative concentration–effect curves for the vanilloid receptor 1 agonists capsaicin (■, $n=6$), resiniferatoxin (▼, $n=6$) and olvanil (●, $n=6$) in guinea pig isolated tracheal smooth muscle. Data are mean ± S.E.M.

Single fiber activity in the airway was discriminated by placing a concentric electrical stimulating electrode on the recurrent laryngeal nerve, through which the majority of fibers enter the trachea. The recording electrode was placed within the ganglion and manipulated until single unit activity was detected. When electrically evoked action potentials were seen, the stimulator was switched off and the trachea and bronchi were gently brushed with a von Frey filament. Mechanically sensitive receptive fields were revealed when a burst of action potentials was elicited in response to von Frey filament stimulation. Conduction velocities were determined by electrically stimulating the receptive field and monitoring the time elapsed between the shock artifact and the recorded action potential. This delay was divided by the distance between the receptive field and the recording electrode to yield a conduction velocity. C-fibers were identified as having conduction velocities of <1 m/s.

2.5. Data analysis

Data were expressed as arithmetic mean ± S.E.M. Contraction in guinea pig isolated tracheal preparations were expressed as a percentage of contraction induced by 30 mM $BaCl_2$ ($BaCl_2$ Max) added at the end of the experiment. The responses of C-fibers were presented as the peak frequency (highest number of action potentials recorded in 1 s) of arrival of action potentials at cell bodies in the jugular ganglion. Data were compared using a Students paired or non-paired *t*-test where appropriate. Statistical significance of means was compared by analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. $P<0.05$ was considered statistically significant.

2.6. Drugs and reagents

Capsaicin, resiniferatoxin, histamine chloride, indomethacin and $BaCl_2$ were obtained from Sigma (St. Louis, MO). Olvanil was obtained from Tocris (Ballwin, MO). Histamine was dissolved in KBS. $BaCl_2$ was dissolved in distilled water. VR1 agonists were dissolved and diluted in absolute ethanol and 10 μl was added to tissue baths. Indomethacin was dissolved in absolute ethanol (50 mM) and added to KBS to give a final concentration of 10 μM.

3. Results

3.1. Isometric tension recording

Capsaicin (1–10 μM) evoked concentration-dependent contractions of guinea pig isolated tracheal smooth muscle (Fig. 1). The threshold concentration of capsaicin was ≥ 1 nM. A maximally effective concentration of capsaicin (1 μM) evoked a response equivalent to 85 ± 4% ($n=6$) of $BaCl_2$ Max. Consistent with previous studies, the estimated EC_{50} for capsaicin was 17.3 ± 1.3 nM ($n=6$).

Resiniferatoxin (0.1–1.0 μM) evoked concentration-dependent contractions of guinea pig isolated tracheal smooth muscle (Fig. 1). The threshold concentration of resiniferatoxin was ≥ 0.1 nM. A maximally effective concentration of resiniferatoxin (100 nM) evoked a response equivalent to 68 ± 4% ($n=6$) of $BaCl_2$ Max. Consistent with previous studies, the estimated EC_{50} for resiniferatoxin was 1.3 ± 1.3 nM ($n=6$).

The vanilloid VR1 receptor agonist olvanil (1–10 μM) was a weak spasmogen of guinea pig isolated tracheal smooth muscle. The highest concentration of olvanil studied (10 μM) resulted in a contraction equivalent to only 11 ± 5% ($n=7$) of $BaCl_2$ Max (Fig. 1).

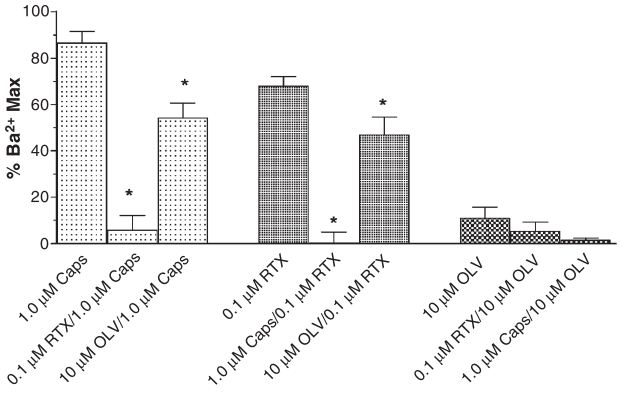

Fig. 2. Cross-desensitization effects in guinea pig tracheal strips. Vanilloid receptor 1 agonist alone values are from the concentration response curve (Fig. 1). Pre-incubation with vanilloid receptor 1 agonist was carried out as described in Section 2. (OLV/CAPS = olvanil pre-incubation, followed by capsaicin; RTX/CAPS = resiniferatoxin pre-incubation, followed by capsaicin; OLV/RTX = olvanil pre-incubation, followed by resiniferatoxin; CAPS/RTX = capsaicin pre-incubation, followed by resiniferatoxin; CAPS/OLV = capsaicin pre-treatment, followed by olvanil; RTX/OLV = resiniferatoxin pre-treatment, followed by olvanil) Data are mean ± S.E.M. $^{**}P<0.01$.

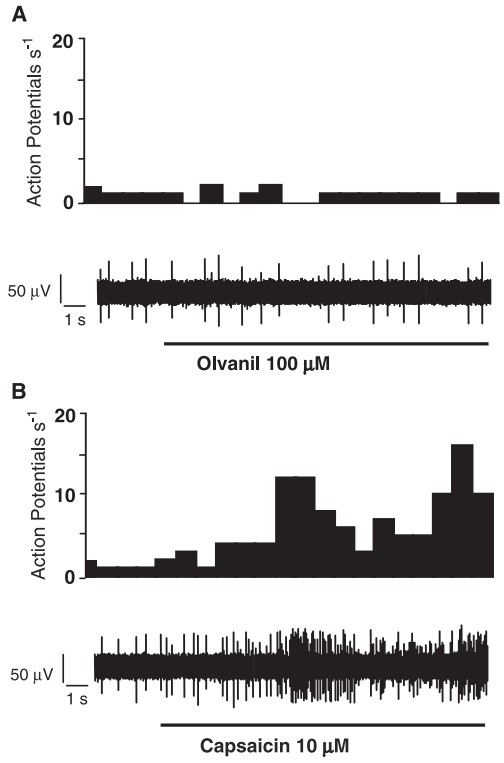

Fig. 3. Typical extracellular recording traces and histograms showing the effect of olvanil (A) and capsaicin (B) on action potential discharge in a C-fiber (estimated conduction velocity = 0.78 m/s) whose receptive field was located in a guinea pig isolated trachea. Application of olvanil was not associated with an increase of the low level of spontaneous activity in this fiber. In contrast, application of capsaicin was associated with a vigorous discharge of action potentials.

3.2. Desensitization studies

Pre-incubation with olvanil (10 μM) prior to addition of capsaicin (1 μM) produced contractions which were 54 ± 6% of the $BaCl_2$ Max (Fig. 2, $n = 7$, $P < 0.01$ vs. contraction to 1.0 μM capsaicin during the concentration response curve). In tissues pre-incubated with resiniferatoxin (100 nM), addition of 10 μM capsaicin produced contractions which were 6 ± 6% of $BaCl_2$ Max (Fig. 2, $n = 5$, $P < 0.01$ vs. contraction to 1.0 μM capsaicin during the concentration response curve).

Pre-treatment with olvanil resulted in contractions to 100 nM resiniferatoxin which were 47 ± 8% $BaCl_2$ Max (Fig. 2, $n = 6$, $P < 0.05$ vs. contraction to 100 nM resiniferatoxin during the concentration response curve). In contrast, addition of resiniferatoxin (100 nM) after pre-incubation with 1.0 μM capsaicin produced contractions which were 0.3 ± 5% of $BaCl_2$ Max (Fig. 2, $n = 6$, $P < 0.01$ vs. contraction to 100 nM resiniferatoxin during the concentration response curve).

Pre-incubation with either 100 nM resiniferatoxin or 1.0 μM capsaicin prior to addition of 10 μM olvanil produced a slight decrease in contraction (5 ± 4% $BaCl_2$ Max after resiniferatoxin, 0.8 ± 1% $BaCl_2$ Max after capsaicin, $n = 6$ for both (Fig. 2)). However, these were not statistically different from 10 μM olvanil in the concentration response curve.

3.3. Electrophysiological studies

Capsaicin-sensitive C-fibers whose receptive fields were located in the trachea and whose cell bodies resided in the jugular ganglion were studied (mean conduction velocity, 0.8 ± 0.2 m/s, $n = 4$). Perfusion of the tracheal–bronchial preparation with KBS containing 10 μM olvanil (15 min exposure) did not evoke action potential discharge in any of the fibers tested (Fig. 3A). However, even after a 15-min exposure to 10 μM olvanil, C-fibers were still electrically excitable (Fig. 4A) and all fibers recorded from responded vigorously to capsaicin (1 μM; Fig. 3B) either as a 200 μl bolus applied directly to the receptive field ($n = 1$) or by addition of capsaicin to the KBS perfusing the tracheal compartment of the recording chamber ($n = 3$). In the latter case, within 10 min of continuous exposure to capsaicin (1 μM) all C-fibers ceased responding to capsaicin and two of these were no longer responsive to mechanical or electrical stimulation of their receptive fields (Fig. 4B). The mean peak frequency of the action potential discharge evoked by capsaicin (1 μM) was 24 ± 7 action potentials s^{-1} ($n = 4$).

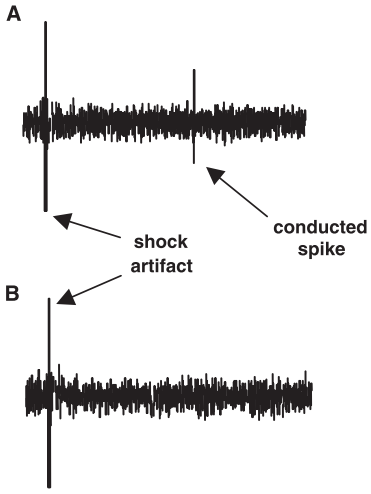

Fig. 4. Typical extracellular recording traces showing the influence of (A) olvanil and (B) capsaicin on the electrical excitability of a C-fiber receptive field (same fiber as in Fig. 3, estimated conduction velocity = 0.78 m/s) that was located in a guinea pig isolated trachea. Prior to (not shown) and following application of olvanil (10 μM) for 15 min (A), a supramaximal electrical stimulus (20 V, 0.8 ms duration) applied to the receptive field resulted in a shock artifact and a delay of 78 ms prior to the arrival of a conducted spike recorded with an extracelluar electrode placed near the cell body of this fiber in the jugular ganglion. In contrast, after a 10-min perfusion with KBS containing capsaicin (1 μM), application of an electrical stimulus (150 V, 0.8 ms duration) to the receptive field resulted in a shock that was not associated with the arrival of spike, suggesting that capsaicin blocked the ability of this fiber to generate or conduct action potentials.

4. Discussion

The main finding of this study was that the structurally related vanilloid VR1 receptor agonists capsaicin, resiniferatoxin and olvanil exhibited striking differences in their ability to excite C-fibers. It is well established that the excitatory action of capsaicin on C-fibers peripheral terminals evokes both action potential discharge and the release of neuropeptides. Our findings suggest that, in stark contrast to capsaicin and resiniferatoxin, the vanilloid VR1 receptor agonist olvanil does not excite the afferent or efferent function of C-fiber peripheral terminals in guinea pig airways. Moreover, prolonged exposure to olvanil produced only a modest inhibition in the ability of these fibers to respond to capsaicin or resiniferatoxin. In contrast, resiniferatoxin and capsaicin were able to almost completely desensitize to one another in agreement with previous work (Ellis and Undem, 1994).

Capsaicin-induced contraction of guinea pig isolated airway smooth muscle is dependent on the release of spasmogenic neurokins from C-fibers innervating the airways (Ellis and Undem, 1994; Maggi et al., 1991). Studies of knockout mice and transfected cells have provided strong evidence that the excitatory actions of capsaicin on sensory neurons are mediated by the vanilloid VR1 receptor, a non-selective cation channel whose activation is blocked selectively by capsazepine or ruthenium red (Caterina et al., 2000). Similarly, capsaicin-induced contraction (Ellis and Undem, 1994; Maggi et al., 1991), neuropeptide release (Lou, 1993) and action potential discharge in guinea pig airway C-fibers (Fox et al., 1995) were inhibited by capsazepine consistent with the expression of vanilloid VR1 receptor immunoreactivity in nociceptive-like tachykinin-containing airway afferent neurons (Myers et al., 2002). Previous studies demonstrated that although less potent than resiniferatoxin, olvanil and capsaicin were similarly potent at evoking vanilloid VR1 receptor-mediated responses in HEK293 cells transfected with the rat or human vanilloid VR1 receptor (Jerman et al., 2000; Smart et al., 2001). Moreover, olvanil, resiniferatoxin and capsaicin were full agonists in these studies (Jerman et al., 2000; Smart et al., 2001). In a recent study using Chinese Hamster Ovary (CHO) cells transfected with guinea pig VR1, olvanil was shown to be more potent than either capsaicin or resiniferatoxin in raising intracellular Ca^{2+} levels (Savidge et al., 2002). Olvanil and capsaicin have been shown to be equipotent in eliciting neuropeptide release from the central terminals of nociceptors in the rat spinal cord (Wardle et al., 1997) and adrenaline secretion in rats (Watanabe et al., 2001) via the activation of vanilloid VR1 receptors. In contrast, we found marked differences in the ability of these compounds to evoke contraction in guinea pig airways. Our observation that olvanil did not induce significant contraction of guinea pig isolated trachea indicates that olvanil, unlike capsaicin or resiniferatoxin, does not induce appreciable release of neuropeptides from the peripheral terminals of C-fibers within guinea pig airways. These findings are indicative of significant differences in the relative sensitivity of vanilloid VR1 receptor transfected HEK293 or CHO cells and the peripheral terminals of airway capsaicin-sensitive C-fibers to the vanilloid VR1 receptor agonists capsaicin, resiniferatoxin and olvanil.

In addition to evoking neuropeptide release, activation of vanilloid VR1 receptors also evokes action potential discharge in C-fibers. We used single unit electrophysiological recording to compare the relative ability of capsacin and olvanil to evoke action potential discharge in guinea pig airway C-fibers. We found that olvanil, at a concentration at least 10-fold greater than that required to evoke a maximal vanilloid VR1 receptor-mediated response in transfected HEK293 and CHO cells (Jerman et al., 2000; Smart et al., 2001), failed to evoke action potential discharge in airway C-fibers whose receptive fields we identified in guinea pig isolated airways. In contrast, the application of capsaicin to these receptive fields during, or following exposure to olvanil, evoked action potential discharge in every C-fiber tested. Combined with our contraction studies, these findings suggest that olvanil did not activate the afferent or efferent function of capsaicin-sensitive C-fibers within guinea pig airways.

One possible explanation for our observation that capsaicin, but not olvanil, excited guinea pig airway C-fibers is that olvanil may be more potent at inhibiting, rather than activating, C-fibers. Indeed, olvanil was shown to inhibit potassium-induced release of calcitonin gene-related peptide (CGRP)-like immunoreactivity from the central terminals of nociceptors in rat spinal cord (Dickenson et al., 1990) and to induce analgesia without initial activation of nociceptors (Dray and Dickenson, 1991). However, in the current study, prior exposure to high concentrations of olvanil (10 μM) had only a minimal inhibitory effect on capsaicin or resiniferatoxin-induced contractions. Similarly, our electrophysiological studies of C-fibers demonstrated that these fibers were still capable of supporting action potentials and responded vigorously to capsaicin even after prolonged (20 min) exposure to 10 μM olvanil. Thus, it would appear that the inability of olvanil to excite the afferent or efferent function of capsaicin-sensitive C-fibers was not due an inhibitory action of this compound.

There are a number of reports describing qualitatively and quantitatively different responses of sensory neurons to olvanil and capsaicin. For example, in rat trigeminal ganglion neurons, the membrane depolarization produced by capsaicin is rapid, while that produced by olvanil or resiniferatoxin is slow (Liu et al., 1997; Liu and Simon, 1998). Dickenson et al. (1990) demonstrated that olvanil did not activate the peripheral terminals of C-fibers in rat skin or tail, however, olvanil was nearly as potent as capsaicin at eliciting CGRP release from the central terminals of nociceptors (Wardle et al., 1997). Capsaicin was similarly potent at both sites (Dickenson et al., 1990; Wardle et al., 1997). In contrast, olvanil was 10-fold more potent than capsaicin in

activating neuropeptide-mediated increases in blood flow in rabbit skin (Hughes et al., 1992). In the nucleus of the solitary tract, olvanil fails to activate neurons but is able to desensitize to resiniferatoxin (Geraghty and Mazzone, 2002). Taken together with our current data, it would appear that although capsaicin and olvanil evoke similar vanilloid VR1 receptor-mediated responses in transfected HEK293 and CHO cells (Jerman et al., 2000; Smart et al., 2001), as well as in Ca^{2+} uptake assays in dorsal root ganglion neurons (Walpole and Wrigglesworth, 1993), these assays are not predictive of the ability of vanilloid VR1 receptor agonists to evoke the afferent and efferent function of C-fibers or their ability to desensitize these responses.

The differing abilities of olvanil and capsaicin to evoke action potential discharge or neuropeptide from C-fibers are difficult to reconcile with the established similarity and efficacy of these compounds on human and rat cloned vanilloid VR1 receptor. The existence of vanilloid receptor subtypes which are heterogeneously distributed among the central and peripheral C-fibers terminals is a possibility, although strong pharmacological or molecular evidence for capsaicin-sensitive vanilloid receptor subtypes is lacking (Szallasi and Blumberg, 1999; Szallasi et al., 1999). Alternatively, the different kinetics of olvanil and capsaicin-evoked ion currents in sensory neurons may be responsible (Liu et al., 1997).

In a recent study examining tissue selectivity of anandamide and olvanil (Andersson et al., 2002), it was observed that these two vanilloid VR1 receptor agonists were able to elicit full agonist responses in guinea pig mesenteric artery but were weak partial agonists in guinea pig bronchi. Andersson et al. (2002) suggested that the lack of effect of these vanilloid VR1 receptor agonists is due to the absence of a transport system necessary for olvanil and anandamide, but not capsaicin to enter the cells to access the vanilloid VR1 receptor intracellular agonist binding site in the peripheral terminals of capsaicin-sensitive C-fibers in bronchi. In contrast, afferent nerve terminals within the mesenteric artery express the anandamide transporter, that carriers both olvanil and anandamide into the nerve terminal, allowing them to access the vanilloid VR1 receptor intracellular agonist binding site (Andersson et al., 2002). Taken together, these data suggest that the relative absence of a response to olvanil in the present study may be due to a lack of access of olvanil to the vanilloid VR1 receptor agonist binding site. If this is the case, it would be consistent with our findings that olvanil neither activated nor fully desensitized vanilloid VR1 receptor mediated responses in guinea pig airway C-fibers.

In conclusion, our findings demonstrate that the vanilloid VR1 receptor agonist olvanil neither stimulates tachykinin release nor evokes action potential discharge in capsaicin-sensitive C-fibers in guinea pig airways. Moreover, olvanil was ineffective at blocking the excitability of C-fibers and caused only modest inhibition of the contractile response to both capsaicin and resiniferatoxin in isolated guinea pig trachea. These findings are in stark contrast to the similar potency and efficacy of olvanil and capsaicin in evoking vanilloid VR1 receptor-mediated responses in other tissue and cell types and demonstrate the importance of the experimental system used to compare activities of vanilloid VR1 receptor agonists.

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