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Linalool suppresses voltage-gated currents in sensory neurons and cerebellar Purkinje cells

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Summary. Linalool is a major component of essential oils and possesses various biological effects in sensory or central nervous systems. To investigate the pharmacological and biophysical effects of linalool on voltage-gated currents in sensory neurons, we used the whole-cell patch clamp and the Ca^{2+} imaging techniques. Under the voltage clamp, membrane depolarization generated time- and voltage-dependent current responses in newt olfactory receptor cells (ORCs). Linalool significantly and reversibly suppressed the voltage-gated currents in ORCs. The dose-suppression relation of linalool for the voltage-gated Na^{+} current could be fitted by the Hill equation with a half-blocking concentration of 0.56 mM and a Hill coefficient of 1.2. To test whether linalool suppresses voltage-gated currents in ORCs specifically or suppresses currents in other neurons generally, we next examined the effects of linalool on voltage-gated currents in newt retinal neurons and rat cerebellar Purkinje cells. Linalool suppressed the voltage-gated currents not only in retinal horizontal cells and ganglion cells but also in Purkinje cells. Furthermore, bath application of linalool inhibited the KCl-induced $[Ca^{2+}]_i$ response of ORCs, suggesting that linalool suppresses Ca^{2+} currents in ORCs. These results suggest that linalool non-selectively suppresses the voltage-gated currents in newt sensory neurons and rat cerebellar Purkinje cells.

Keywords: Olfactory receptor cell, retina, linalool, patch clamp, voltage-gated current, newt.

Introduction

The fragrance of essential oils induces psychological and physiological changes in human. Various types of volatile components in essential oils are determined using chromatography. Linalool is a major component of essential oils such as jasmine and lavender, and possesses various biological activities in the sensory or central nervous system. The inhalation of linalool induces sedative effects in

vertebrates including humans (Buchbauer et al., 1991; Sugawara et al., 1998). Linalool affects the human brain beta wave (Sugawara et al., 1998) and shows an inhibitory effect on glutamatergic neurons in the rat cerebral cortex (Elisabetsky et al., 1995). Linalool also demonstrates antinociceptive activities in mice, involving ATP-sensitive K^+ channels, which play an important role in the mechanisms of pain modulation (Peana et al., 2004). However, the pharmacological effect of linalool on voltage-gated channels has not yet been investigated.

Olfactory receptor cells (ORCs) convey chemosensory information to the olfactory bulb, and express various types of ionic channels such as voltage-gated Na^+, Ca^{2+} and K^+ channels on their somatic membrane (Schild and Restrepo, 1998). In the present study, we investigated the pharmacological effects of linalool on voltage-gated currents in newt ORCs using whole-cell patch clamp and calcium imaging techniques. To further characterize the general effects of linalool on voltage-gated channels, we used another sensory system, the retina, since voltage-gated channels in retinal neurons have been well-characterized (Lipton and Tauck, 1987; Tachibana, 1983). Although linalool is not a stimulant for or an endogenous molecule in the retina, it would be interesting to elucidate biophysical and pharmacological properties of linalool against voltage-gated channels.

Materials and methods

Preparation and patch-clamp recording procedures

ORCs and retinal neurons were dissociated enzymatically from the olfactory epithelium or the retina of the newt, *Cynops pyrrhogaster* as previously reported (Kawai et al., 1996; Kawai and Miyachi, 2000b). The mucosae excised from the olfactory cavity and isolated retinae were incubated for 5 min at 30°C in a Ringer solution containing 0.1% collagenase (Sigma, St Louis, MO) and 5–7 units/ml papain (Sigma), respectively, with no added Ca^{2+} and Mg^{2+}. The tissue was then rinsed three times and triturated with a control Ringer solution (in mM): 110 Na^+, 2.6 K^+, 3 Ca^{2+}, 10 HEPES, 10 glucose, and 10 ppm phenol red (pH adjusted to 7.4 with KOH).

Wister rat (postnatal day 14–20) were anesthetized and decapitated, and cerebella were dissected out and minced in ice-cold Krebs solution (in mM): 124 NaCl, 5 KCl, 1.2 KH_2PO_4, 2.4 $CaCl_2$, 1.3 $MgSO_4$, 26 $NaHCO_3$, and 10 glucose. The solution was continuously oxygenated with 95% O_2, 5% CO_2. After preincubation in Krebs solution for 40 min at 31°C, the tissue was digested first in Krebs solution containing 0.01% Pronase (Calbiochem-Novabiochem, La Jolla, CA) for 25 min at 31°C and then in solution containing 0.01% thermolysin (type X, Sigma) for 25 min at 31°C (Matsushita et al., 2002). Tissue was withdrawn as needed and triturated with a fire-polished Pasteur pipette to liberate individual neurons. All experiments were performed in accordance with the guidelines of the Society for Neuroscience.

Isolated cells were plated on concanavalin A-coated glass coverslips and viewed on an upright microscope (Olympus, BX51WI, Tokyo, Japan) with differential interference contrast optics (40× water-immersion objective). Purkinje cells were identified by their large diameter and characteristic pear shape attributable to the stump of the dendritic tree. Membrane currents were recorded with the whole-cell recording configuration (Hamill et al., 1981) using a patch-clamp amplifier (Axon Instruments, Axopatch 200B, Foster City, CA) linked to a computer. Recording procedures were controlled by pCLAMP software (Axon Instruments). Data were low-pass filtered (4-pole Bessel type) with a cutoff frequency of 5 kHz and then digitized at 10 kHz by an analog-to-digital interface. All experiments were performed at room temperature (23–25°C).

The recording pipette for newt sensory neurons was filled with a pseudo-intracellular (K^+) solution (in mM): 116 KCl, 1 $CaCl_2$, 5 EGTA, and 10 HEPES, or Cs^+ solution: 116 CsCl,

1 $CaCl_2$, 5 EGTA, and 10 HEPES. The pipette solutions were adjusted with KOH or CsOH to pH 7.4. Pipette resistance was about 6 MΩ. The pipette solution for rat Purkinje cells contained (in mM): 140 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 EGTA, 2 Mg-ATP, 10 HEPES and 10 ppm phenol red (pH adjusted to 7.3 with KOH). The solution used to record newt Na^+ currents contained (in mM): 80 NaCl, 2.6 KCl, 1 $CoCl_2$, 35 tetraethylammonium (TEA) chloride, 10 HEPES, and 10 glucose. Linalool (Sigma) was dissolved in solution also containing 0.2% dimethylsulfoxide (DMSO) and was applied through the bath.

Intracellular Ca^{2+} measurements

The Fura-2-based calcium imaging technique was similar to that reported previously (Ohkuma et al., 2002). Isolated cells were incubated with 5 μM Fura 2-AM (Molecular Probes, Eugene, OR) for 30 min at room temperature in a Ringer solution containing 0.1% Pluronic F-127 (Sigma). For recording Fura 2-loaded cells, the recording chamber was mounted on the stage of an inverted fluorescent microscope (Nikon, Diaphot TMD300, Tokyo, Japan) with phase contrast optics (20× dry objective). Fura-2 was excited by UV-range radiation from a Xenon lamp. Images were taken by alternate excitations at 340 and 380 nm, and reflected by a 400 nm dichroic mirror. The fluorescence signal was filtered at 510 ± 20 nm, and detected by a digital CCD camera (Hamamatsu Photonics, ARGUS-50/CA, Hamamatsu, Japan). Ratio images were analyzed using ARGUS-50/CA software. A high KCl (40 mM) extracellular solution was made by isotonic replacement of NaCl and used to stimulate calcium entry to the cells by membrane depolarization.

Results

Linalool non-selectively suppressed the voltage-gated currents in newt ORCs. The isolated ORCs had a resting membrane potential of -70 ± 9 mV ($n = 19$) and an input resistance of 3.8 ± 0.2 GΩ ($n = 10$). In control Ringer solution, depolarizing step pulses from the holding potential (V_h) of −100 mV induced time- and voltage-dependent currents (Fig. 1A). At step voltages between −90 mV and +40 mV, current responses consisted of a transient inward current (<15 ms) and a delayed outward current. The initial transient inward current was blocked by bath application of 3 mM linalool and the late sustained outward current was reduced as well (Fig. 1B). Similar phenomena were observed in all cells recorded ($n = 13$). The current showed recovery after washout of linalool (Fig. 1C). A linalool-free solution containing 0.2% DMSO did not change the membrane currents significantly. Figure 1D and E show the current–voltage (I–V) relation of transient inward currents and delayed outward currents recorded from the same cell as in Fig. 1A–C. The transient inward current was prominent at the command voltage of −20 mV and the delayed outward current was activated beyond −20 mV. These currents were suppressed by 3 mM linalool (Fig. 1D, E; filled circle).

Transient inward currents such as the voltage-gated Na^+ current (I_{Na}) are essential in the generation of action potentials in ORCs. To examine the effect of linalool on I_{Na} in newt ORCs, I_{Na} was isolated using pharmacological agents. In the experiment seen in Fig. 2A, depolarizing step pulses ($V_h = -100$ mV) induced a rapidly decaying I_{Na} in the odorant-free solution. Bath application of 3 mM linalool suppressed I_{Na} (Fig. 2B). Suppression of I_{Na} was observed in all voltage ranges recorded (Fig. 2C; $n = 10$). To determine the effective concentration of linalool on I_{Na}, the recorded cells were exposed to several concentrations of linalool. Figure 2D shows the dose-response curve of linalool ($n = 8$). As the concentration of linalool was increased, the peak amplitude of I_{Na} was

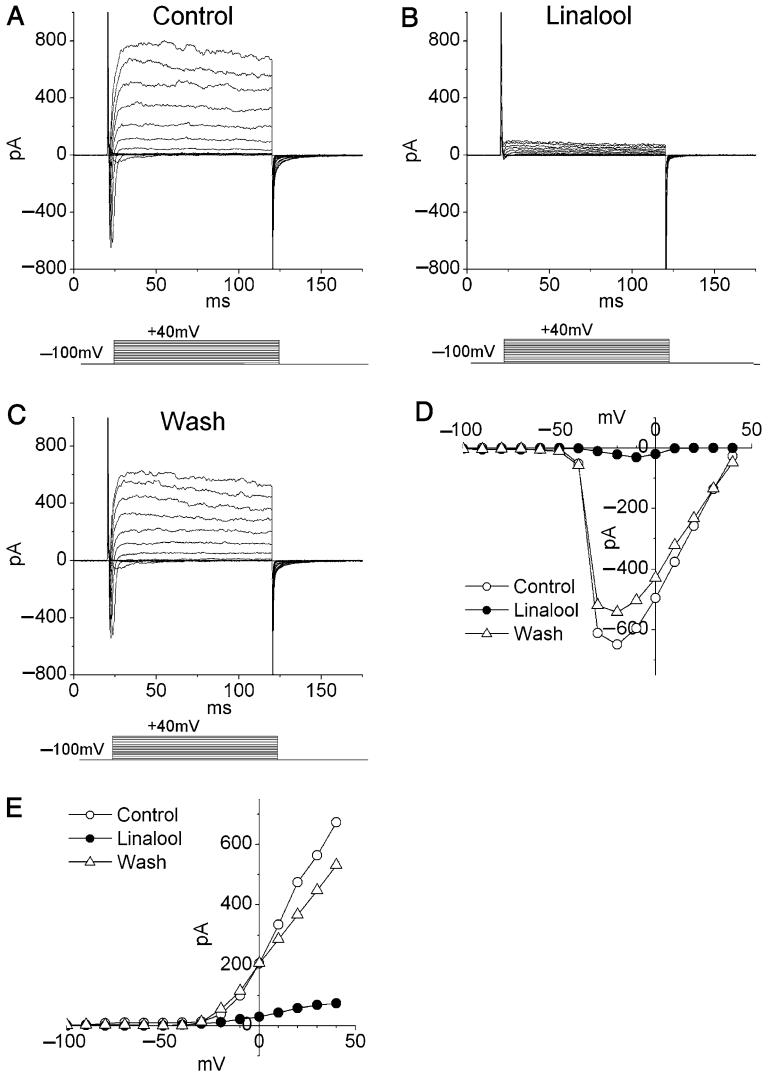

Fig. 1. Linalool suppresses membrane currents of an isolated newt olfactory receptor cell. **A** Membrane currents were induced by depolarization from V_h of −100 mV. Command voltages were increased in 10 mV steps from −90 mV to +40 mV. The cell was bathed in the control Ringer solution and the recording pipette was filled with K^+ solution. **B** Membrane currents induced by the same depolarization as in **A** in the presence of 3 mM linalool in the bath. **C** Membrane currents measured after washout of linalool. **D** I–V relation of the transient inward currents recorded from the same cell as in **A**–**C**. Peak amplitude under the control (open circle), 3 mM linalool (filled circle), and washout (open triangle) conditions were measured during each voltage step and plotted against the command voltage. **E** I–V relation of outward currents recorded from the same cell as in **A**–**C**. The outward currents measured at 100 ms of each voltage step were plotted with identical symbols as in **D**

reduced. The data were fitted by the Hill equation with a half-blocking concentration (IC_{50}) of 0.56 mM and a Hill coefficient of 1.2.

Does linalool specifically suppress voltage-gated currents in ORCs or suppress currents in general in other neurons? To investigate this, we next examined the effects of linalool on voltage-gated currents in newt retinal neurons.

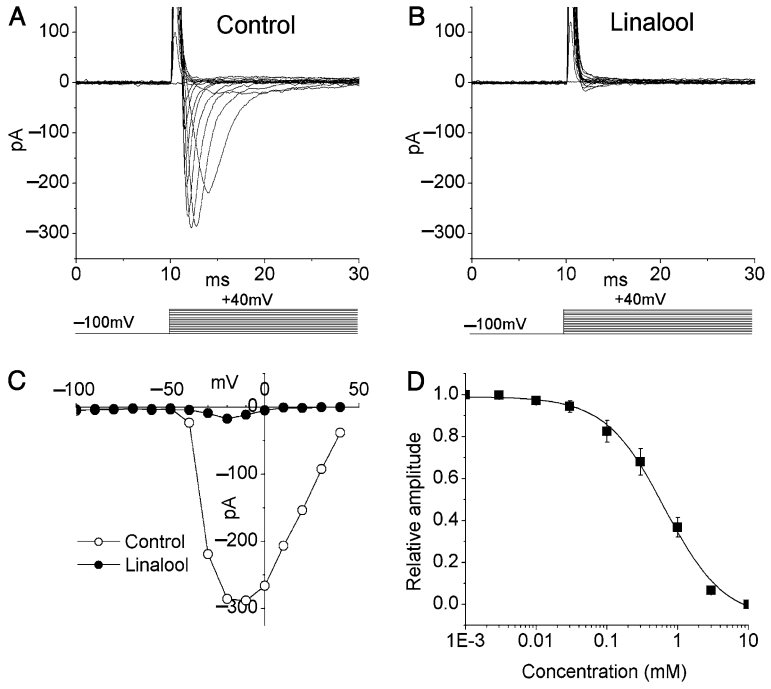

Fig. 2. Effects of linalool on a voltage-gated Na^+ current (I_{Na}) of isolated ORCs. **A** I_{Na} evoked by depolarization from V_h of -100 mV. Command voltages were increased in 10 mV steps from -90 mV to $+40$ mV. The cell was bathed in the control solution containing 1 mM $CoCl_2$ to block voltage-gated Ca^{2+} current and 35 mM TEA to block K^+ current. The recording pipette was filled with Cs^+ solution. **B** Membrane currents induced by the same depolarization as in **A** in the presence of 3 mM linalool in the bath. **C** I–V relation of I_{Na} recorded from the same cell as in **A** and **B**. Peak amplitude under the control (open circle) and 3 mM linalool (filled circle) conditions were measured during each voltage step. **D** Dose-response curve of I_{Na}. Current amplitude at the command voltage of -20 mV ($V_h = -100$ mV) was normalized and plotted as a function of linalool concentration. Data points are mean responses across cells ($\pm$S.E.M., $n = 8$). The continuous line shows a least squares fit of the data to the Hill equation

Isolated horizontal cells had a resting membrane potential of -37 ± 6 mV ($n = 5$) and an input resistance of 270 ± 30 MΩ ($n = 5$). In control Ringer solution, a sustained inward current of approximately 150 pA was observed at the V_h of -60 mV in a horizontal cell (Fig. 3A). Hyperpolarizing pulses between -100 mV and -70 mV evoked large steady inward currents (Fig. 3A), and anomalous rectification was prominent below the command voltage of -40 mV (Fig. 3C). Membrane depolarization beyond -10 mV induced an outward current (Fig. 3A, C). The voltage-gated currents in retinal horizontal cells have been well-characterized (Tachibana, 1983). These currents are known to consist of an L-type Ca^{2+} current ($I_{Ca,L}$), a delayed rectifier K^+ current (I_K), a fast transient K^+ current (I_A), and an anomalous rectifier K^+ current (I_{Ka}) (Tachibana, 1983). Bath application of 3 mM linalool almost completely suppressed the steady inward current at V_h of -60 mV and also suppressed the currents evoked by the voltage pulses over the entire voltage range (Fig. 3B, C; $n = 4$). Thus, linalool non-selectively suppressed the voltage-gated currents in retinal horizontal cells.

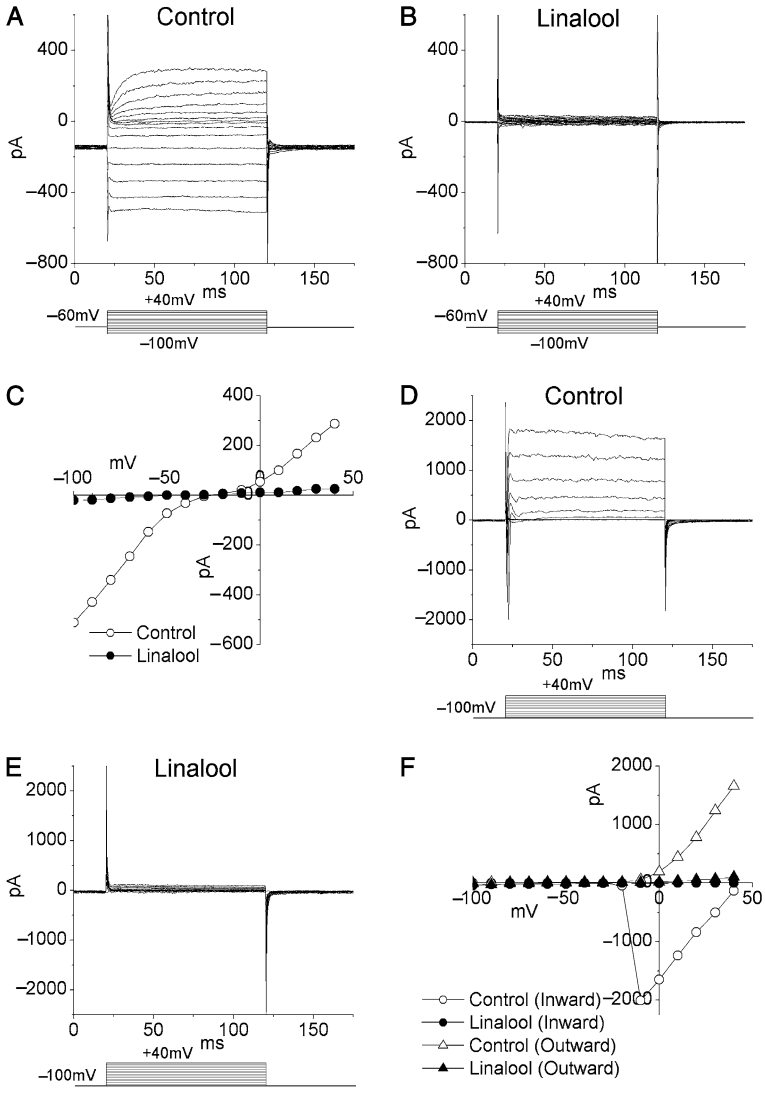

Fig. 3. Linalool suppresses membrane currents in newt retinal neurons. **A** Membrane currents of an isolated retinal horizontal cell were induced by depolarization from V_h of −60 mV. Command voltages were increased in 10 mV steps from −100 mV to +40 mV. The cell was bathed in the control Ringer solution and the recording pipette was filled with K^+ solution. **B** Membrane currents of the same horizontal cell induced by the same depolarization as in **A** in the presence of 3 mM linalool in the bath. **C** I–V relation of membrane currents recorded from the same cell as in **A** and **B**. The currents under the control (open circle) and 3 mM linalool (filled circle) conditions were measured at 100 ms in **A** and **B** and plotted against the command voltage. **D** Membrane currents of an isolated retinal ganglion cell were induced by depolarization from V_h of −100 mV. Command voltages were increased in 10 mV steps from −90 mV to +40 mV. The bath and pipette solutions were the same as in **A**. **E** Membrane currents of the same ganglion cell induced by the same depolarization as in **D** in the presence of 10 mM linalool. **F** I–V relation of the transient inward and sustained outward currents recorded from the same cell as in **D** and **E**. The amplitude of the inward current was measured at the peak under the control (open circle) and linalool (filled circle) conditions. The amplitude of the sustained outward current was measured at 100 ms under the control (open triangle) and linalool (filled triangle) conditions

Linalool also suppressed the voltage-gated currents in retinal ganglion cells. The isolated ganglion cells had a resting membrane potential of -71 ± 4 mV ($n = 5$) and an input resistance of 1.7 ± 0.3 GΩ ($n = 5$). In control Ringer solution, depolarizing step pulses from V_h of -100 mV induced time- and voltage-dependent currents (Fig. 3D). At step voltages between -90 mV and $+40$ mV, current responses consisted of a transient inward current (<10 ms) and a delayed outward current (Fig. 3D). These currents are known to consist of I_{Na}, $I_{Ca,L}$, I_K, I_A, and Ca^{2+}-activated K^+ current ($I_{K(Ca)}$) (Lipton and Tauck, 1987). Bath application of 10 mM linalool suppressed the initial transient

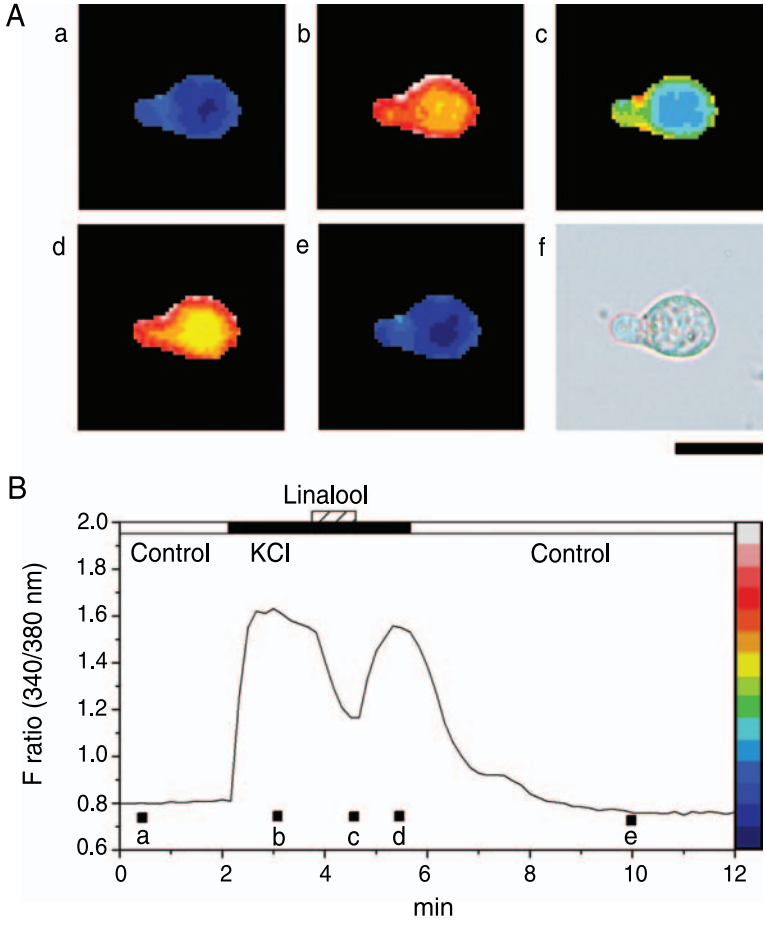

Fig. 4. Linalool suppresses KCl-induced $[Ca^{2+}]_i$ increase in isolated ORCs. **A** Sequential images of $[Ca^{2+}]_i$ changes were recorded from a Fura 2-loaded ORC. The fluorescence ratio images were acquired under the control Ringer solution (**a**), high KCl (40 mM) solution (**b**), high KCl containing 3 mM linalool (**c**), high KCl (**d**), and then washout (**e**) conditions. The images in **a**–**e** were taken at times corresponding to points marked with filled rectangles above the trace in **B**. The pseudocolor scale representing the 256 gray levels of the 340/380 nm ratios is shown in **B**; white indicates the largest changes. (**f**) Phase-contrast image of the same cell as in **a**–**e**. Scale bar, 20 μm. **B** The time course of the spatially averaged $[Ca^{2+}]_i$ in the same cell as in **A**. Application of 40 mM KCl (black bar) induced $[Ca^{2+}]_i$ increase in the cell. Following application of 40 mM KCl, 3 mM linalool (diagonal bar) inhibited the KCl-induced $[Ca^{2+}]_i$ response. The KCl response returned to resting level after washout of the cell (white bar)

inward current and the late sustained outward current over the entire voltage range (Fig. 3E, F; $n = 5$).

In the somatic membrane of the newt ORC, two types of voltage-gated calcium currents (I_{Ca}) have been identified ($I_{Ca,L}$ and T-type Ca^{2+} current ($I_{Ca,T}$)) (Kawai et al., 1996). To examine the effect of linalool on I_{Ca} in newt ORCs, we used the Fura-2-based calcium imaging technique. Figure 4 shows a typical example of the $[Ca^{2+}]_i$ changes in response to linalool in an ORC. After the addition of high KCl (40 mM) solution to the bath, the $[Ca^{2+}]_i$ rapidly increased from the resting level (Fig. 4Ab, B). Immediately following the addition of the high KCl solution, ORC was superfused with the high KCl solution containing 3 mM linalool. Linalool markedly reduced $[Ca^{2+}]_i$ ($44.9 \pm 2.6\%$, $n = 43$) in newt ORCs (Fig. 4Ac, B). The effect of linalool was reversible (Fig. 4Ad, B). The KCl-induced $[Ca^{2+}]_i$ response returned to the resting level after washout of the cell (Fig. 4Ae, B). This suggests that linalool also suppresses I_{Ca} in the ORCs.

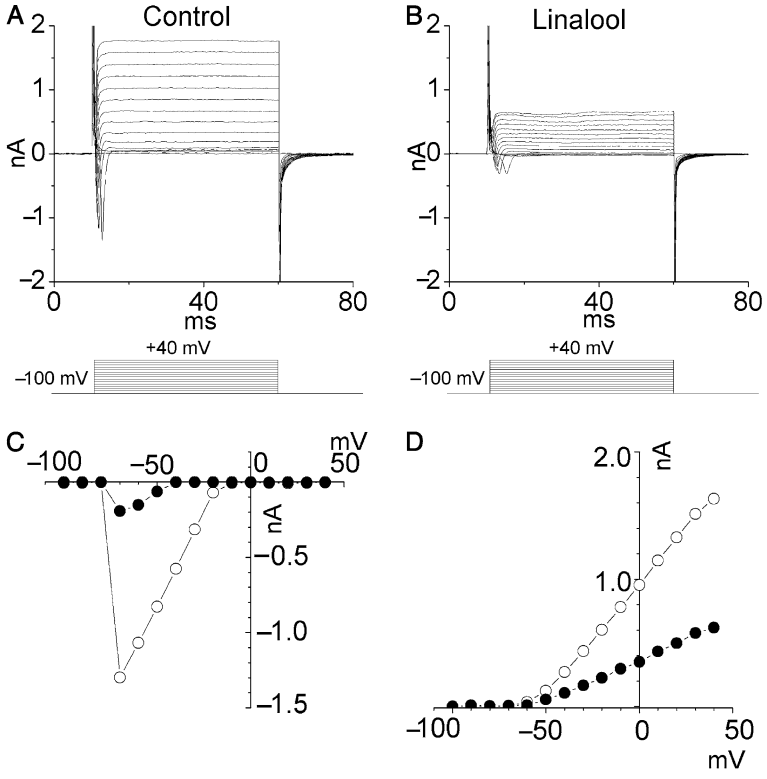

Fig. 5. Linalool reduces membrane currents of an isolated rat cerebellar Purkinje cell. **A** Membrane currents were induced by depolarization from V_h of -100 mV. Command voltages were induced in 10 mV steps from -90 mV to $+40$ mV. **B** Membrane currents induced by the same depolarization as in (**A**) in the presence of 10 mM linalool in the bath. **C** I–V relation of the transient inward currents recorded from the same cells as in (**A**, **B**). Peak amplitude under the control (open circle), 10 mM linalool (filled circle) conditions were measured during each voltage step and plotted against the command voltage. **D** I–V relation of outward currents recorded from the same cell as in (**A**, **B**). The outward currents measured at 50 ms of each voltage step were plotted with identical symbols as in (**C**)

In order to test whether linalool also suppresses voltage-gated currents in mammalian neurons of outside of the sensory system, we next examined the effects of linalool on rat cerebellar Purkinje cells. Linalool non-selectively suppressed the voltage-gated currents in rat Purkinje cells as well. In control Ringer solution, depolarizing step pulses from V_h of -100 mV induced time- and voltage-dependent currents (Fig. 5A). At step voltages between -90 mV and $+40$ mV, current responses consisted of a transient inward current and a delayed outward current. The initial transient inward current was inhibited by bath application of 10 mM linalool and the sustained outward current was reduced as well (Fig. 5B). Similar phenomena were observed in all cells recorded ($n = 5$). Figure 5C and D show the I–V relation of transient inward currents and delayed outward currents recorded from the same cell as in Fig. 5A, B. These currents were markedly reduced by linalool (Fig. 5C, D; filled circle). Thus, linalool suppresses voltage-gated currents not only in newt sensory neurons but also in mammalian non-sensory neurons.

Discussion

In the present study we studied the pharmacological effects of linalool on the voltage-gated currents in isolated ORCs and retinal neurons. We found that linalool non-selectively suppresses the voltage-gated currents (I_{Na}, $I_{Ca,L}$, $I_{Ca,T}$, I_K, and $I_{K(Ca)}$) in newt ORCs. Similar suppression has been reported in newt ORCs and in goldfish retinal horizontal cells in response to odorants such as amyl acetate, acetophenone, and limonene (Kawai, 1999a, b; Kawai et al., 1997; Kawai and Miyachi, 2000b). The IC_{50} of linalool against I_{Na} in newt ORCs was 0.56 mM (Fig. 2D). This value was larger than that of amyl acetate recorded in previous experiments ($IC_{50} = 0.11$ mM; Kawai et al., 1997). The difference in the odorant's structure and its accessibility to the binding site in the ionic channels would cause the variation in the blocking effects.

The mechanism for the unspecific block of voltage-gated channels by linalool is still unclear in the present study. However, linalool shows high lipid solubility in common with various other odorants such as amyl acetate, acetophenone, and limonene. Thus, it is likely that linalool can interfere with the lipids of somatic membranes and can affect ionic channels directly as those other odorants reported previously (Kawai, 1999a, b; Kawai et al., 1997; Kawai and Miyachi, 2000b). Indeed, those odorants block not only voltage-gated channels but also ligand-gated channels such as glutamate-gated channels (Ohkuma et al., 2002) and cyclic nucleotide-gated channels (Kawai and Miyachi, 2000a; Kurahashi et al., 1994).

The KCl-induced $[Ca^{2+}]_i$ response was markedly, but not completely, reduced by 3 mM linalool (Fig. 4), while $I_{Ca,L}$ and $I_{Ca,T}$ were almost completely blocked by 3 mM amyl acetate (Fig. 4 in Kawai et al., 1997). The weaker effect of linalool on the KCl-induced $[Ca^{2+}]_i$ response may suggest that linalool suppresses only voltage-gated Ca^{2+} channels on the somatic membrane, but does not affect the mechanism of intracellular Ca^{2+} signaling including Ca^{2+}-induced Ca^{2+} release in ORCs.

Linalool also suppresses the voltage-gated currents ($I_{Ca,L}$, I_K, I_A, and I_{Ka}) in retinal horizontal cells and those (I_{Na}, $I_{Ca,L}$, I_K, I_A, and $I_{K(Ca)}$) in retinal ganglion cells. This result represents the first data to prove that an odorant blocks I_{Na} in neurons outside of the olfactory system. Although linalool is neither a stimulant for nor an endogenous molecule in the retina, linalool suppresses various types of voltage-gated currents in retinal neurons. These observations are similar to the action of odorants on the ligand-gated currents in ORCs and retinal neurons (Kawai and Miyachi, 2000a; Kurahashi et al., 1994; Ohkuma et al., 2002), and to that of local anesthetics on the voltage-gated currents in various preparations (Butterworth and Strichartz, 1990; Hille, 1977). Thus, we suggest that linalool directly blocks both olfactory and retinal voltage-gated channels and affects the voltage gating in sensory neurons in general. In addition, linalool also suppressed the voltage-gated channels in rat cerebellar Purkinje cells. Therefore, it is likely that linalool blocks the voltage-gated channels not only in newt sensory neurons but also in mammalian non-sensory neurons.

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