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Research report

Dopamine modulates a voltage-gated calcium channel in rat olfactory receptor neurons

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Abstract

Dopamine D2 receptors exist in the soma of rat olfactory receptor neurons. Actions of dopamine on the voltage-gated Ca^{2+} channels in the neurons were investigated using the perforated whole-cell voltage-clamp. In 10 mM Ba^{2+} solution, rat olfactory receptor neurons displayed the inward currents elicited by the voltage ramp (167 mV/s) and depolarizing step pulses from a holding potential of −91 mV. The inward Ba^{2+} currents were greatly reduced by 10 μM nifedipine (L-type Ca^{2+} channel blocker). The Ba^{2+} currents were inhibited by the external application of dopamine. The IC_{50} for the inhibition was about 1 μM. Quinpirole (10 μM, a D2 dopamine agonist) also inhibited the Ba^{2+} currents. Quinpirole did not affect the activation and inactivation kinetics of the Ba^{2+} currents. The results suggest that dopamine modulates the L-type Ca^{2+} channels in rat olfactory receptor neurons via the mechanism independent of voltage.

Theme: Sensory systems

Topic: Olfactory senses

Keywords: D2 receptor; Ca^{2+} channel; Quinpirole; Nifedipine

1. Introduction

Rat olfactory mucosa is innervated by sympathetic nerve fibers and the relatively higher level of norepinephrine (NE) and lower level of dopamine are found in the mucosa [23]. Catecholamine levels in rat nasal mucus can be modulated by noxious stimuli [26]. The depletion of NE in olfactory bulb affected no significant effect on odor detection performance of rats [9], but epinephrine enhanced odorant contrast in newt olfactory neurons [22]. The intraperitoneal doses of the D2 dopamine receptor agonist (quinpirole) depressed the odor detection performance of rats [8]. In contrast, the injection of the D1 dopamine agonist (SKF 38393) enhanced the performance of rats [10]. However, only dopamine D2 receptors have been identified in mammalian olfactory receptor neurons [3,12,24,27]. Dopamine D2 receptors exist in both the soma and nerve terminal of olfactory receptor neurons, suggesting that odor detection can be modulated at both the mucosa and olfactory bulb. Vargas and Lucero [40] reported that dopamine D2 receptor agonist (quinpirole) modulated the hyperpolarization-activated inwardly rectifying current (I_h) via the inhibition of adenylyl cyclase in cultured rat olfactory receptor neurons. Similarly quinpirole inhibited odorant-induced rise in cAMP [4]. In other neurons, L-type Ca^{2+} currents were enhanced by the activation of adenylyl cyclase–protein kinase A cascade via D1 receptor [36], but the Ca^{2+} currents were depressed by D2 receptor activation [17]. The L-type Ca^{2+} channels are present in rat olfactory receptor neurons [37]. We examined the modulatory action of dopamine on the Ca^{2+} channels. We found that dopamine modulates the L-type Ca^{2+} channels in rat olfactory receptor neurons.

2. Materials and methods

2.1. Cell preparation

Olfactory receptor neurons were isolated from adult Wistar rats, as described before [33]. The experiments

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were performed in accordance with the Guidelines for Animal Experimentation of Nagasaki University. Prior to decapitation, animals were anesthetized by intraperitoneal injection of pentobarbital (30 mg/kg). The olfactory epithelium and supporting cartilage were quickly removed and washed in Ca^{2+}-, Mg^{2+}-free saline containing 2 mM EDTA. The epithelium was completely separated from the cartilage. It was cut into small pieces and incubated for 10 min in 3 ml of the same saline containing 5 mM L-cysteine and 15 units/ml papain (Sigma, St. Louis, MO, USA). After removal of 2 ml of the dissociation solution, the tissue were gently triturated with a heat-polished pipette. Dissociation was terminated by the addition of 3 ml of normal saline solution containing 1 mM Ca^{2+}. Olfactory receptor neurons were readily distinguished by their characteristic bipolar morphology. The dissociated neurons maintained their characteristics for at least 5 h.

2.2. Electrophysiological recording

Voltage-clamp recording was performed in the whole-cell configuration [16] using a CEZ 2300 patch-clamp amplifier (Nihon Kohden, Tokyo, Japan). The patch pipettes were pulled from Pyrex glass capillaries containing a fine filament (Summit Medical, Tokyo, Japan) with a two-stage puller (Narishige PD-5, Tokyo, Japan). The tips of the electrodes were heat-polished with a microforge (Narishige MF-83). The resistance of the resulting patch electrodes was 5–10 MΩ when filled with internal solution. The formation of 5–20 GΩ seals between the patch pipette and the cell surface was facilitated by applying weak suction to the interior of the pipette. Amphotericin B (133 μg/ml, Sigma) was added to the pipette solution when using the perforated method [34]. The perforated whole-cell condition was obtained within 5 min of the establishment of a GΩ seal. Recordings were made from olfactory receptor neurons that had been allowed to settle on the bottom of a chamber placed on the stage of an inverted microscope (Olympus IMT-2, Tokyo, Japan). The recording pipette was positioned with a hydraulic micromanipulator (Narishige WR-88). The current signal was low-pass-filtered at 5 kHz, digitized at 125 kHz using a TL-1 interface (Axon Instruments, Union City, CA, USA), acquired at a sampling rate of 0.25–5 kHz using the pCLAMP 5.5 software (Axon Instruments) and stored on the hard disk of an IBM-compatible personal computer running the pCLAMP. This was also used to control the digital–analogue converter for the generation of the clamp protocol. The indifferent electrode was a chlorided silver wire. All voltages were corrected for the liquid junction potentials (−5 to −11 mV) between the external solutions and Cs^+ internal solution. Capacitance and series resistance were compensated for, as appropriate. The whole-cell current–voltage (*I–V*) relationship was obtained from the current generated by the 70-ms voltage step pulses between −81 and +49 mV in 10- or 20-mV increments from a holding potential of −91 mV or a 167-mV/s voltage ramp from −100 to +100 mV. Input resistance was calculated from the current generated by the voltage step from −91 to −101 mV. Data analyses were performed by using the pCLAMP, Origin 6.1 (OriginLab, Northampton, MA, USA) and SigmaPlot 6.0 (SPSS, Chicago, IL, USA).

2.3. Solutions and drugs

Normal saline solution consisted of (in mM): NaCl, 145; KCl, 5; $CaCl_2$, 1; $MgCl_2$, 1; Na-pyruvate, 1; Hepes, 20; glucose, 5; pH 7.2. The pH of normal saline and other solutions was adjusted by Tris base. The extracellular Ba^{2+} solution for recording the currents through the voltage-gated Ca^{2+} channels contained (in mM): NMDG-Cl, 137; $BaCl_2$, 10; Na-pyruvate, 1; Hepes, 20; glucose, 5; pH 7.2. The solution exchange was done by gravity flow. For stock solutions, dopamine (10 mM, Sigma) and quinpirole (10 mM, Sigma) were dissolved in deionized water. Nifedipine (100 mM, Sigma) was dissolved in dimethylsulphoxide (DMSO). The dopamine solution was made on every experimental day. The stock solutions were frozen at −20 °C. Samples of the stock solutions were added to the Ba^{2+} solution to give the desired final concentration. The Cs^+ internal solution contained (in mM): CsCl, 135; $CaCl_2$, 0.1; $MgCl_2$, 1; EGTA, 1; Hepes, 10; pH 7.2.

All experiments were carried out at room temperature (20–25 °C). Values are presented as means±S.E.M.

3. Results

3.1. Basic properties of the currents through the voltage-gated Ca^{2+} channels in rat olfactory receptor neurons

After attaining the whole-cell configuration in normal saline solution, rat olfactory receptor neurons displayed voltage-gated Na^+ currents in response to the depolarizing voltage steps from a holding potential of −105 mV (data not shown). The outward K^+ currents were eliminated by the replacement of internal K^+ with Cs^+. Further analyses were performed only in the neurons that possessed the voltage-gated Na^+ currents. Rat olfactory receptor neurons also displayed sustained inward currents at a holding potential of −50 mV (Fig. 1A). The current–voltage (*I–V*) relationships were obtained from the current elicited by a 167-mV/s voltage ramp from −100 to +100 mV. Almost linear leak currents were elicited by the voltage ramp in normal saline solution (a in Fig. 1A,B). The ramp protocol was too slow to activate voltage-gated Na^+ currents. When normal saline solution was replaced to 10 mM Ba^{2+} solution (0 mM Na^+), the sustained inward current at −50 mV disappeared. The disappearance might be due to the elimination of external Na^+. In contrast to normal saline solution, the olfactory receptor neurons displayed the

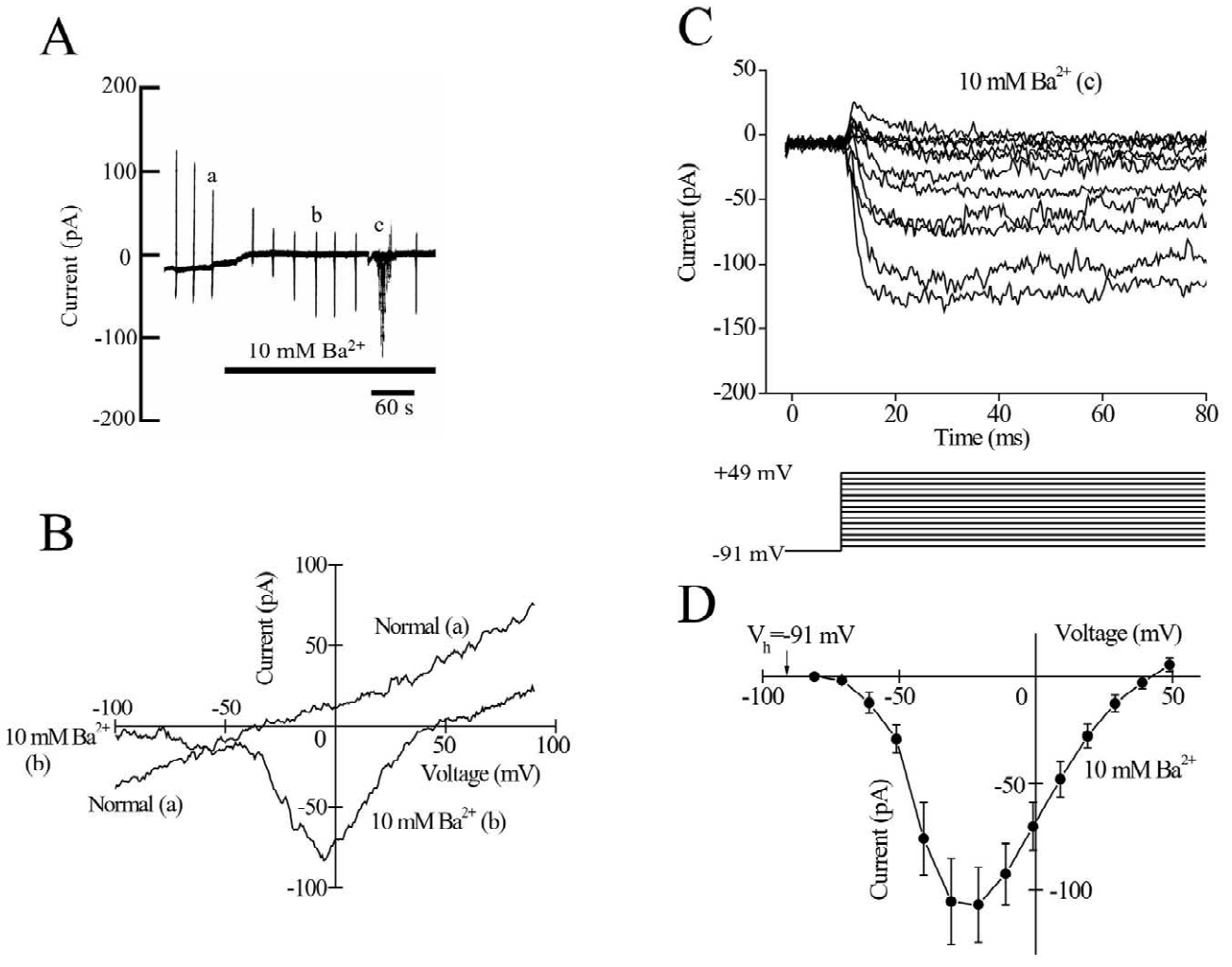

Fig. 1. A representative example of whole-cell current of a rat olfactory receptor neuron in 10 mM Ba^{2+}. (A) The pen recording of the current signal. (B) The plots of whole-cell current–voltage (I–V) relationships produced by a voltage ramp (167 mV/s) from −100 to +100 mV. (C) Sustained inward currents were elicited in response to 70-ms voltage steps between −81 and +49 mV in 10-mV increments from a holding potential of −91 mV. The leak currents were not subtracted from the current traces. The transient capacitative currents could not be completely compensated at positive voltages. (D) Pooled current–voltage (I–V) relationships for the inward Ba^{2+} currents ($n=15$) elicited by the voltage steps. The leak-subtracted data were plotted. The I–V relationships labeled a and b and current traces labeled c were obtained at the times indicated by the same letters on the pen recording. In other figures, similar presentation and labeling are used. In this and all other figures, current recordings were made with perforated whole-cell technique.

distinctive inward current elicited by the voltage ramp between −100 and +100 mV (b in Fig. 1A,B) in 10 mM Ba^{2+} solution. There was no obvious contribution of any inward current in normal saline solution over the voltage range where the inward Ba^{2+} current was apparent. Although we could not find Ca^{2+} currents in normal saline solution using the ramp protocol, small sustained inward currents (−5 to −10 pA) were elicited by a voltage step to −45 mV from a holding potential of −105 mV in five of 15 cells in normal saline solution (data not shown). In the presence of 10 mM Ba^{2+}, sustained inward currents showing little desensitization were elicited by 70-ms voltage pulses that stepped in 10-mV increments from a holding potential of −91 mV (Fig. 1C). Peak inward current of −106.7±17.5 pA ($n=15$) was calculated from the I–V relationships (Fig. 1D). The activation threshold for the inward Ba^{2+} current was about −60 mV and the peak existed between −30 and −10 mV.

The inward Ba^{2+}currents elicited by the voltage ramp were greatly inhibited by 10 μM nifedipine (L-type Ca^{2+} channel blocker). Nifedipine (10 μM) decreased the peak amplitude to 13±8% of the controls in three of three cells (Fig. 2B). A similar result was obtained by the step pulse protocol (Fig. 2C,D). Our results suggest that most of the Ba^{2+} current in rat olfactory receptor neurons may be the current through L-type Ca^{2+} channels, as already described [37]. We rarely observed small transient Ba^{2+} currents (−25 to −40 pA) elicited by a voltage step to −64 mV from a holding potential of −124 mV in three of seven cells (data not shown).

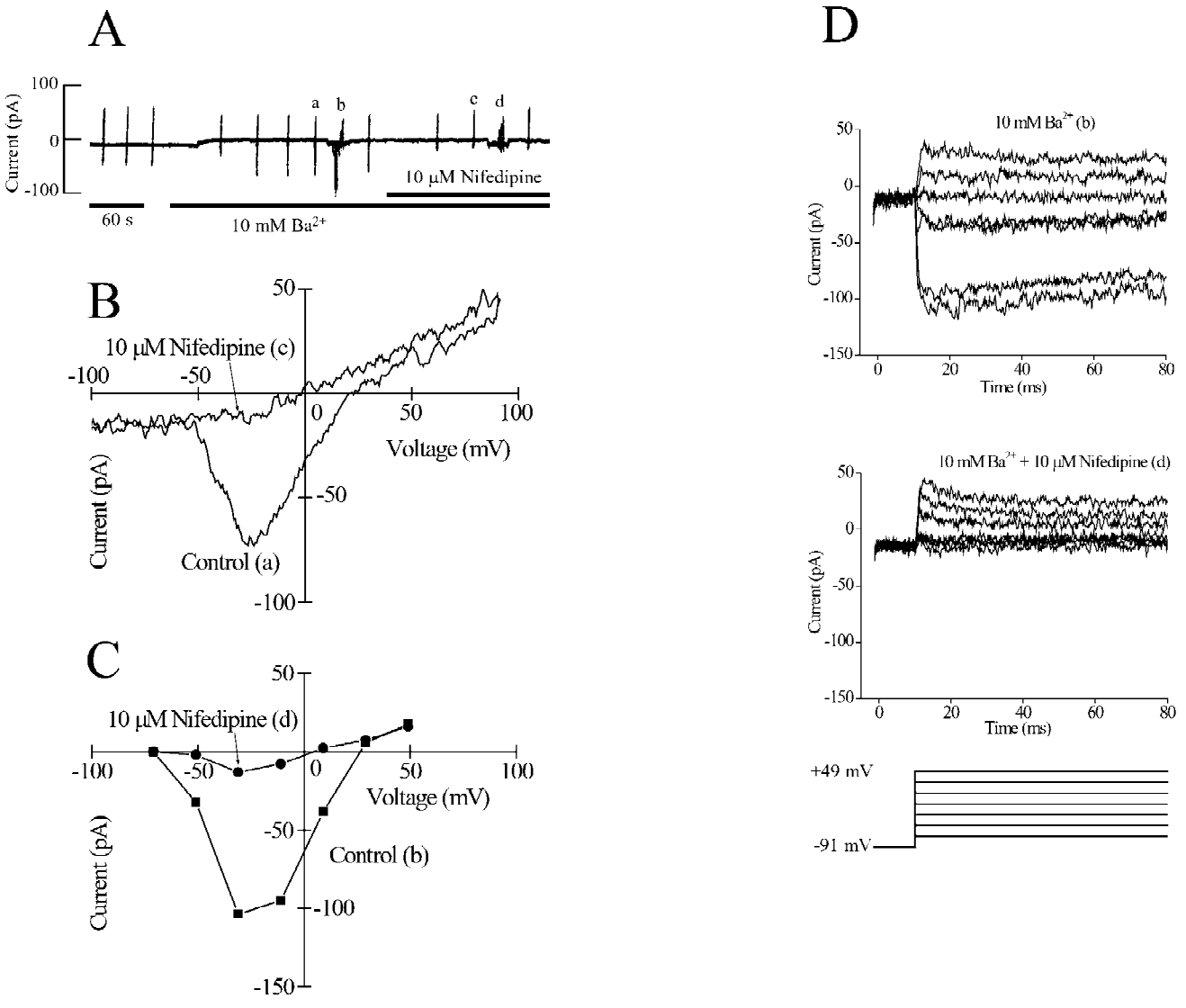

Fig. 2. Effect of nifedipine on the inward Ba^{2+} currents. (A) The pen recording of the current signal. (B) The plots of the whole-cell *I–V* relationships produced by a voltage ramp (167 mV/s) from −100 to +100 mV. (C) The plots of the whole-cell *I–V* relationships produced by the 70-ms step pulses in 20-mV increments between −71 and +49 mV from a holding potential of −91 mV. (D) Current traces plotted in (C).

3.2. Effects of dopamine and quinpirole on the inward Ba^{2+} currents

When 10 μM dopamine were added to external Ba^{2+} solution, the inward Ba^{2+} currents in olfactory receptor neurons gradually decreased (Fig. 3A). Dopamine (10 μM) decreased the peak current to 34±5% of the controls in nine of 20 cells (Fig. 3B,C). The concentration–response curve for the inhibitory effect of dopamine on the Ba^{2+} current is shown in Fig. 3C. The IC_{50} for the inhibition was about 1 μM. Dopamine (10 μM) also decreased the inward Ba^{2+} current elicited by a step pulse from −91 to −21 mV to 36±6% of the controls in four of 11 cells (Fig. 3D). Even when the external solution was returned to 10 mM Ba^{2+} solution without dopamine, the Ba^{2+} current did not recover to initial level after a 5-min wash-out. The Ba^{2+} current maintained its magnitude for at least 15 min in 10 mM Ba^{2+} solution without dopamine, suggesting that the effects of dopamine are not simple due to current rundown.

It has been reported that rat olfactory receptor neurons express D2 dopamine receptors [3,4,24,27]. We examined the effect of quinpirole (a D2 dopamine agonist) on the inward Ba^{2+} current in rat olfactory receptor neurons. Quinpirole (10 μM) greatly inhibited the Ba^{2+} current. The voltage ramp-evoked inward Ba^{2+} current decreased to 31±5% of the controls in 10 of 19 cells (Fig. 4B). The peak Ba^{2+} current elicited by a step pulse from −91 to −21 mV decreased to 24±6% of the controls in five of 12 cells (Fig. 4C,D).

The activation property determined from the data of current–voltage (*I–V*) relationships for the inward Ba^{2+}

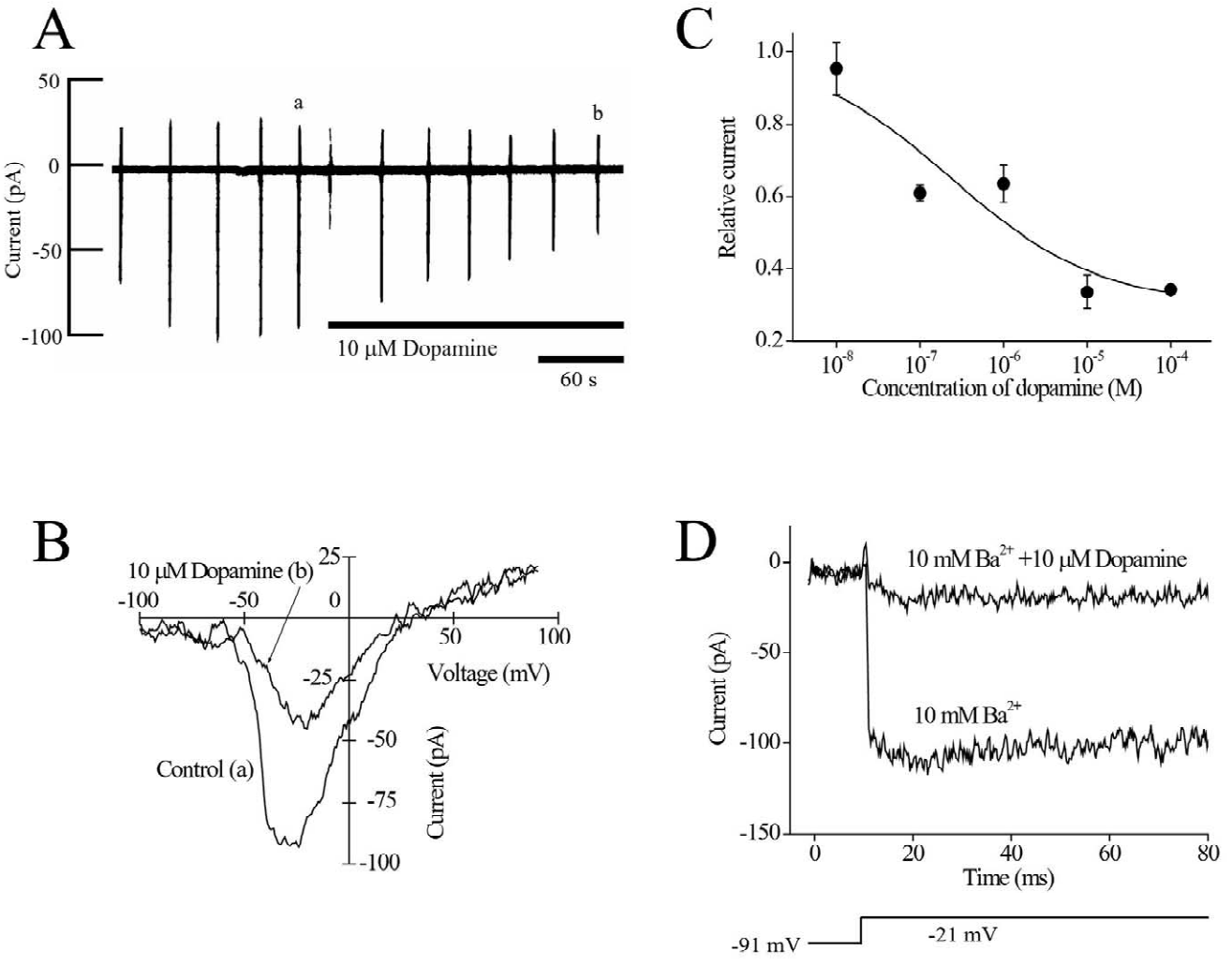

Fig. 3. Effect of dopamine on the inward Ba^{2+} currents. (A) The pen recording of the current signal. (B) The plots of the whole-cell *I–V* relationships produced by a voltage ramp (167 mV/s) from −100 to +100 mV. (C) Dose–response relationship of dopamine on the Ba^{2+} currents elicited by the voltage ramp. The values are means±S.E.M. obtained from three to nine neurons. (D) Current traces in response to a 70-ms voltage step to −21 mV from a holding potential of −91 mV. The data in (A) and (D) were sampled in different neurons.

currents is shown in Fig. 5A. A Boltzmann equation fitted to the points yielded estimates for the voltage of half-maximum activation ($V_{1/2}=-41.6$ mV) and for the Boltzmann inverse slope factor ($k=-5.9$ mV) in 10 mM Ba^{2+} solution without quinpirole. The voltage of half-maximum activation ($V_{1/2}$) and the slope factor (k) in 10 mM Ba^{2+} solution with 10 μM quinpirole were −41.3 and −7.7 mV, respectively. Quinpirole (10 μM) did not change the voltage dependence of the Ba^{2+} currents ($n=4$) (Fig. 5A). The voltage-dependence of steady-state inactivation was studied in a conventional manner by applying 1-s conditioning pulses over a range between −111 and −1 mV to a step to −21 mV. As the level of the conditioning pulses was shifted to the depolarizing direction, the magnitude of the inward currents decreased (Fig. 5B). The resulting curve for the inactivation was fitted with a Boltzmann equation. The point of half-maximum inactivation ($V_{1/2}$) was −53.2 mV in 10 mM Ba^{2+} solution without quinpirole and −53.5 mV in 10 mM Ba^{2+} solution with 10 μM quinpirole. Thus, quinpirole (10 μM) did not affect the inactivation kinetics of the Ba^{2+} currents ($n=5$) (Fig. 5B)

4. Discussion

We could record a sustained inward current of rat olfactory receptor neurons in response to depolarization in 10 mM Ba^{2+} solution, as already described [37]. The inward Ba^{2+} currents were blocked by 10 μM nifedipine, suggesting the expression of the L-type Ca^{2+} channels in rat olfactory receptor neurons. Similarly the L-type Ca^{2+} channels have been identified in olfactory receptor neurons in amphibians [6,13,21,35,38], fishes [5,29,31], lobster [28]. In contrast, newt olfactory neurons displayed the

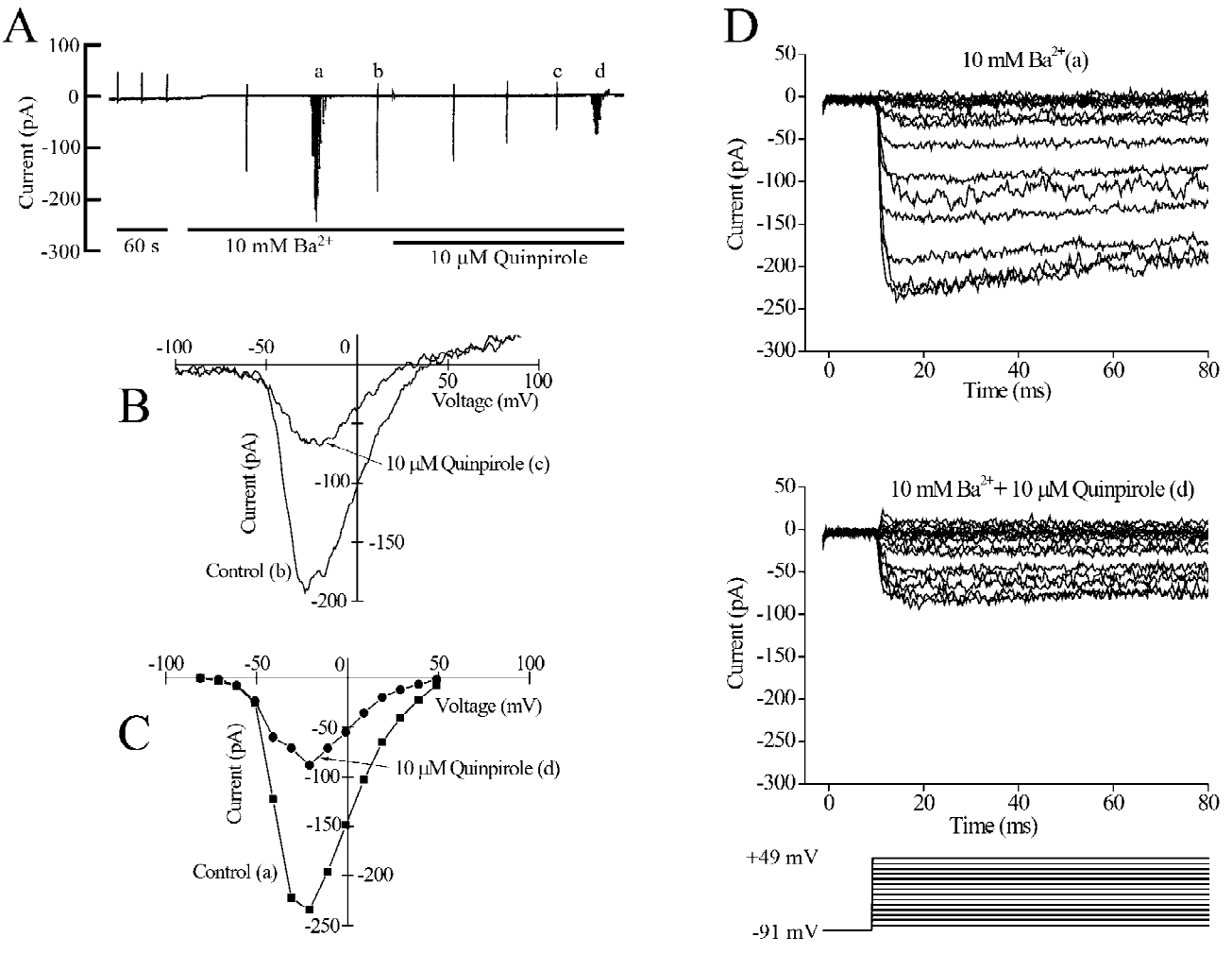

Fig. 4. Effect of quinpirole on the inward Ba^{2+} currents. (A) The pen recording of the current signal. (B) The plots of the whole-cell *I–V* relationships produced by a voltage ramp (167 mV/s) from −100 to +100 mV. (C) The plots of the whole-cell *I–V* relationships produced by the 70-ms step pulses in 10-mV increments between −81 and +49 mV from a holding potential of −91 mV. (D) Current traces plotted in (C).

stable expression of transient T-type Ca^{2+} channel [21]. The receptor neurons in vomeronasal organ also possessed T-type Ca^{2+} channel [20,25,39]. The activation threshold (−60 mV) and maximum voltage (−30 to −10 mV) for the inward Ba^{2+} current in the present experiments were a little lower than the values (activation threshold, −40 to −30 mV; maximum voltage, −10 to +10 mV) reported by the other studies (Fig. 1D). We cannot exclude the expression of the Ca^{2+} channels other than the L-type in rat olfactory receptor neurons, although the Ba^{2+} currents were almost completely blocked by 10 μM nifedipine.

In neurons, dopamine inhibits N-type and P/Q-type Ca^{2+} channels [14]. The inhibitory effect is due to the voltage-dependent prolongation of activation kinetics and the effect is relieved by the positive prepulse [18]. The modulation is induced by the interaction between the G protein βγ complex and the channel [42]. On the other hand, dopamine induces the voltage-independent inhibition of L-type Ca^{2+} channels [14]. Similarly, the L-type Ca^{2+} channels in rat olfactory receptor neurons also could be modulated by dopamine and a D2 agonist (quinpirole). In slice preparation of rat olfactory bulb, it was reported that dopamine D2 receptor mediates presynaptic inhibition of olfactory nerve terminals [1,11,19]. The inhibition was due to the modulation of the presynaptic N-type and P/Q-type Ca^{2+} channels. In the present experiments, isolated olfactory receptor neurons did not contain the nerve terminals. We could not, therefore, observe the voltage-dependent prolongation of activation kinetics in our preparations. We found another effect of dopamine on L-type Ca^{2+} channels that may exist in the dendrite and soma. The D2 receptor activation in rat olfactory epithelium is ascribed to the inhibition of adenylyl cyclase activity [4,27]. It is possible that the modulation of Ca^{2+} channels in rat olfactory receptor neurons is due to the inhibition of adenylyl cyclase elicited by the D2 receptor activation. Quinpirole (10 μM) did not affect the activation and inactivation kinetics of the Ba^{2+} current. The results suggest that quinpirole may elicit the voltage-independent and metabolism-dependent modulation of the Ca^{2+} channels in

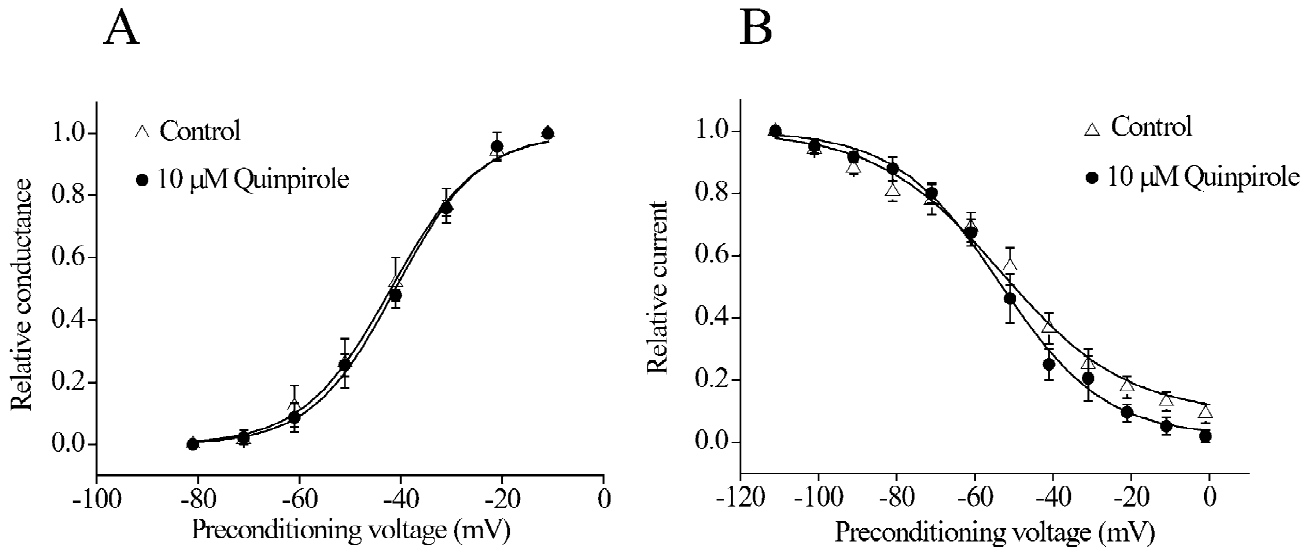

Fig. 5. (A) Voltage dependence of activation of the Ba^{2+} currents. The dependence was determined by *I–V* relationships for the inward Ba^{2+} currents elicited by the voltage steps. Smooth curves are simple Boltzmann functions ($V_{1/2} = -41.7$ mV, $k = -5.9$ mV for the control, $V_{1/2} = -41.3$ mV, $k = -7.7$ mV for 10 μM quinpirole).The values are means±S.E.M. obtained from four neurons. (B) Voltage dependence of steady-state inactivation of the inward Ba^{2+} currents. The dependence was determined by measuring peak current elicited by a single depolarization to −21 mV from a range of 1 s conditioning voltages. Smooth curves are simple Boltzmann functions ($V_{1/2} = -53.2$ mV, $k = 15.9$ mV for the control, $V_{1/2} = -53.5$ mV, $k = 13.2$ mV for 10 μM quinpirole). The values are means±S.E.M. obtained from five neurons.

rat olfactory receptor neurons. Although we did not analyze the mechanism of dopamine effect further, dopamine may modulate the L-type Ca^{2+} channel that is dependent on Gβγ protein activation of a PLCβ-signaling cascade and mobilization of intracellular Ca^{2+} [17]. PLCβ2 subtype was identified in rat olfactory receptor neurons [32]. Further study must be done to know the dopamine effect on the Ca^{2+} channels of rat olfactory receptor neurons. Kawai et al. [22] reported that T-type Ca^{2+} channels were inhibited by epinephrine via cAMP-PKA cascade in amphibian olfactory receptor neurons. Similar results were observed by Wenzel et al. [41] in rat olfactory receptor neurons.

The action of voltage-gated Ca^{2+} channels is similar to that of the receptors at cell surface. The receptors are coupled to intracellular signal transduction pathways. The opening of Ca^{2+} channels allows Ca^{2+} to enter the cell, resulting in the rise of intracellular Ca^{2+} concentration. The rise triggers the activation of ion channels, such as Ca^{2+}-activated K^+ and Cl^- channels [15,30]. These events may influence the excitability of neurons. Dopamine may modulate the excitability of olfactory receptor neurons via the inhibition of L-type Ca^{2+} channels. The Ca^{2+} increase also induces the kinase activation and gene transcription. It was reported that Ca^{2+} rise near the L-type Ca^{2+} channels activates the Ras/MAPK cascade via a Ca^{2+}–calmodulin complex [7]. It is known that dopamine promotes differentiation of mammalian olfactory neurons via D2 dopamine receptors [2,12]. We speculate that dopaminergic modulation of the L-type Ca^{2+} channels may play a role in neural differentiation.

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