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Simulation Analysis of Effects of Adrenaline on Spike Generation in Olfactory Receptor Cells

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Abstract

Adrenaline is known to affect action potentials induced by the step current injection in an olfactory receptor cell (ORC). It is unclear, however, whether it also modulates action potentials induced by odor stimuli. In the present study, the effects of adrenaline on action potentials in ORCs were investigated quantitatively using a computer simulation. Adrenaline suppressed simulated action potentials induced by step current injection near threshold, and increased spike frequency to strong stimuli by 8–25%. Similar effects were obtained by applying a pseudo-transduction current to a model cell. Surprisingly, adrenaline markedly increased spike frequency to strong stimuli by 30–140%, and increased the slope of the stimulus–response relation compared with that of the step current injection. This suggests that adrenaline enhances odorant contrast in olfactory perception by modulating signal encoding of ORCs.

Introduction

Odorant binding to receptor proteins at the ciliary surface of olfactory receptor cells (ORCs) activates enzymatic cascades (Bakalyar and Read, 1991; Breer and Boekhoff, 1992), inducing transduction currents (Gold and Nakamura, 1987; Firestein, 1992; Restrepo *et al.*, 1996). This initial excitation causes a slow and graded voltage change; its amplitude is dependent on odor concentration (Firestein *et al.*, 1993). A graded receptor potential is then encoded into spike trains that transmit olfactory information to the brain.

Olfactory sensitivities are influenced by adrenaline (Beidler, 1961; Arechiga and Alcocer, 1969; Getchell and Getchell, 1984; Zielinski *et al.*, 1989; Woodhead and Nimmo, 1991). Adrenaline enhances the amplitude of the electro-olfactogram induced by an odorant (Arechiga and Alcocer, 1969). Noradrenaline released from the sympathetic nerve also increases electrical activity in the olfactory nerve (Beidler, 1961). Using the patch-clamp technique, our group showed that adrenaline affects spike generation of ORCs by modulating the Na^+ current (I_{Na}) and T-type Ca^{2+} current ($I_{Ca,T}$) via cAMP (Kawai *et al.*, 1999). Adrenaline increased the slope of the stimulus–response relation for action potentials induced by step current injection. It is unclear, however, whether adrenaline also modulates action potentials induced by odor stimuli, because the time course of the odor transduction current is much slower than that of the step current (Gold and Nakamura, 1987; Kurahashi, 1989; Firestein *et al.*, 1993); gradual membrane depolarization induced by the slow transduction current might inactivate transient inward currents such as I_{Na} and $I_{Ca,T}$.

It is known that application of odorants causes secondary effects by suppressing the voltage-gated ionic currents non-selectively and action potentials in ORCs (Kawai *et al.*, 1997a). Although the IC_{50}s of I_{Na} (110 μM) and $I_{Ca,T}$ (150 μM) for amyl acetate are higher than the $K_{1/2}$ (a half-maximal concentration; 53 μM) of the transduction current (Kawai *et al.*, 1997a; Firestein *et al.*, 1993), concentrations of amyl acetate which are lower than the $K_{1/2}$ of the transduction current suppress I_{Na} and $I_{Ca,T}$ by ~5–20% (Kawai *et al.*, 1997a). Thus, it is difficult to investigate the effects of adrenaline on action potentials induced by odorants (even at low concentrations) with the conventional patch-clamp technique. In the present study, this effect was examined using an ionic current model of ORCs.

Materials and methods

An ionic current model of ORCs proposed in our previous report [cf. Table 1 in (Kawai *et al.*, 1997b)] was used for the present simulations. This model was constructed to describe its ionic currents (Na^+-, T-type Ca^{2+}-, L-type Ca^{2+}- and delayed rectifier K^+ currents) by a program using differential equations similar to the method of Hodgkin and Huxley (Hodgkin and Huxley, 1952). The model equations were

Table 1 A description of I_{Na} and $I_{Ca,T}$ in the newt ORC

I_{Na}; Na^+ current
$I_{Na} = G_{Na} \cdot m_{Na}^3 \cdot h_{Na} \cdot (V - E_{Na})$
$dm_{Na}/dt = \alpha_{Na\_m} \cdot (1 - m_{Na}) - \beta_{Na\_m} \cdot m_{Na}$
$\alpha_{Na\_m} = 0.1 \cdot (-35 - V)/(\exp((35 + V)/-5) - 1)$
$\beta_{Na\_m} = 4 \cdot \exp((V + 60)/-8)$
$dh_{Na}/dt = \alpha_{Na\_h} \cdot (1 - h_{Na}) - \beta_{Na\_h} \cdot h_{Na}$
$\alpha_{Na\_h} = 0.07 \cdot \exp((V + 70)/-10)$
$\beta_{Na\_h} = 1/(\exp((40 + V)/-10) + 1)$
$G_{Na} = 45$ [nS], $E_{Na} = 50$ [mV]

$I_{Ca,T}$; T-type Ca^{2+} current
$I_{Ca,T} = G_{Ca,T} \cdot m_{Ca,T}^3 \cdot h_{Ca,T} \cdot (V - E_{Ca})$
$dm_{Ca,T}/dt = \alpha_{Ca,T\_m} \cdot (1 - m_{Ca,T}) - \beta_{Ca,T\_m} \cdot m_{Ca,T}$
$\alpha_{Ca,T\_m} = 0.04 \cdot (-92 - V)/(\exp((92 + V)/-0.4) - 1)$
$\beta_{Ca,T\_m} = 0.6 \cdot \exp((V + 76)/-13)$
$dh_{Ca,T}/dt = \alpha_{Ca,T\_h} \cdot (1 - h_{Ca,T}) - \beta_{Ca,T\_h} \cdot h_{Ca,T}$
$\alpha_{Ca,T\_h} = 0.014 \cdot \exp((V + 90)/-20)$
$\beta_{Ca,T\_h} = 0.2/(\exp((60 + V)/-10) + 1)$
$G_{Ca,T} = 12$ [nS], $E_{Ca} = 50$ [mV]

Each parameter is equal to that in Kawai *et al.*'s model (Kawai *et al.*, 1997b).

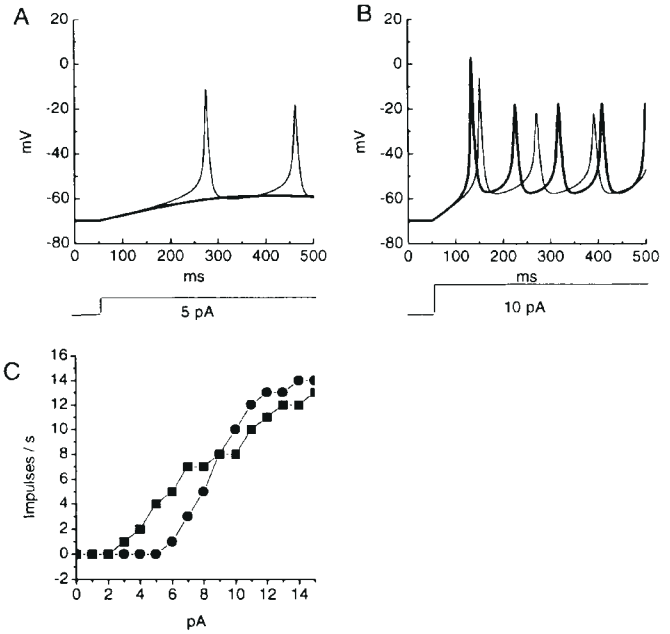

Figure 1 Effects of adrenaline on action potentials of a model ORC induced by step current injections. **(A)** Model responses to near-threshold depolarization by injecting a +5 pA current under control (thin line) and adrenaline conditions (thick line). **(B)** Model responses induced by +10 pA current injection under control (thin line) and adrenaline conditions (thick line). **(C)** The simulated relationship between current injection and spike frequency in control (filled square) and adrenaline conditions (filled circle).

calculated on an IBM-compatible PC by the method of Runge-Kutta (Hamming, 1962) (time step, 10 μs) to give voltage and current values. The conductance of Na^+ or Ca^{2+} channels was determined by the product of the activation parameter (m) and inactivation parameter (h), and that of the K^+ channel was calculated only by the activation parameter (n). A transduction current induced by an odor stimulus was modeled by the alpha function

$$K \cdot t/\tau \cdot \exp(1 - t/\tau) \quad (1)$$

where K is the peak current amplitude and τ is the time constant. Since the time constant of transduction current in newt ORCs is ~400 ms (Kurahashi, 1989), it was approximated with τ of 400 ms.

Results

I first examined the effects of adrenaline on action potentials induced by step current injection using the ORC model. Since adrenaline reduces the conductance of the T-type Ca^{2+} channel in newt ORCs by 33% and shifts the activation curve of the Na^+ channel toward a negative voltage (–4 mV) (Kawai *et al.*, 1999), these effects were incorporated into the ORC model. In the adrenaline condition, $G_{Ca,T}$ in the T-type Ca^{2+} current model (Table 1) was decreased by 33%, and α_{Na_m} and β_{Na_m} in the Na^+ current model were shifted to a negative voltage by 4 mV. Under weakly stimulated conditions (5 pA, Figure 1A), adrenaline suppressed simulated action potentials. To strong stimuli causing repetitive spikes, adrenaline increased spike frequency (Figure 1B). Spike frequency was increased by 8–25% between 10 and 15 pA (Figure 1C). Adrenaline also narrowed the dynamic range and made the stimulus–response relation steeper (Figure 1C). Mean slopes between 5 and 15 pA were 0.9 spikes·s^{-1}·pA^{-1} in the control condition and 1.4 spikes·s^{-1}·pA^{-1} in the adrenaline condition. Adrenaline thus amplified the simulated signal by ~60%. These results are consistent with our previous experimental data (Kawai *et al.*, 1999).

To investigate effects of adrenaline on action potentials induced by odor stimuli, a pseudo-transduction current at various amplitudes (Figure 2A) was injected into the ORC model. The pseudo-transduction current was approximated by alpha functions (see equation 1). Adrenaline also suppressed simulated action potentials induced by the current injection with a weak stimulation (5 pA, Figure 2B). In contrast, adrenaline increased spike frequency with a strong stimulation (10 pA, Figure 2C). Surprisingly, the increased ratio (30–140%) of adrenaline to the control condition between 8 and 15 pA (Figure 2D) was markedly larger than that (8–25%) obtained by the simulation of the step current injection (Figure 1C). Adrenaline also narrowed the dynamic range and made the simulated stimulus–response relation steeper. Mean slopes between 5 and 15 pA were 0.25 spikes·s^{-1}·pA^{-1} in the control condition and 0.75 spikes·s^{-1}·pA^{-1} in the adrenaline condition. Adrenaline thus amplified the signal by ~3-fold. This result suggests that the adrenergic system may work to enhance odorant contrast by modulating signal encoding of ORCs.

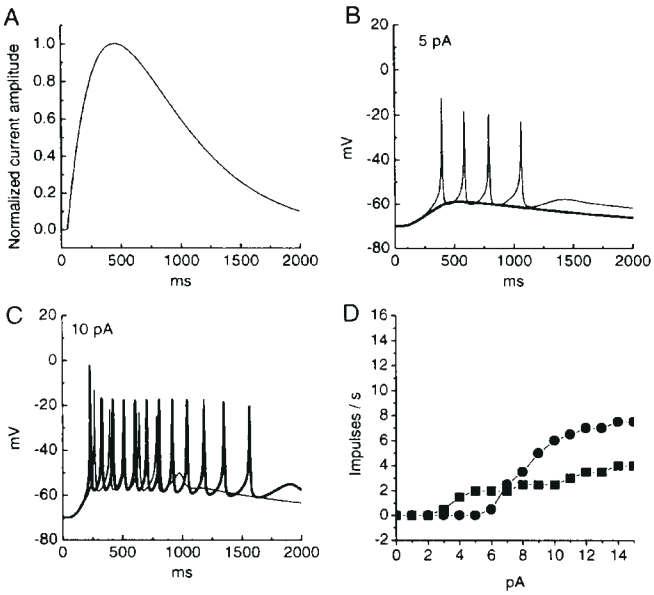

Figure 2 Effects of adrenaline on simulated action potentials induced by injecting a pseudo-transduction current of various amplitudes. **(A)** Normalized pseudo-transduction current. Its time course was approximated by an alpha function (equation 1). **(B)** Model responses to a depolarization by injecting a +5 pA current under control (thin line) and adrenaline conditions (thick line). **(C)** Model responses induced by + 10 pA current injection under control (thin line) and adrenaline conditions (thick line). **(D)** The simulated relationship between current injection and spike frequency in control (filled square) and adrenaline conditions (filled circle).

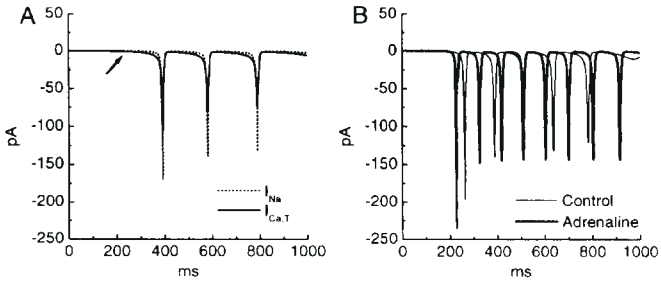

Figure 3 Simulated ionic current responses during the action potential induced by pseudo-transduction current injections. **(A)** Simulated $I_{Ca,T}$ (solid line) and I_{Na} (dotted line) responses to a pseudo-transduction current injection of +5 pA during the control action potential shown in Figure 2B. Current responses are shown on a fast time scale. **(B)** Simulated I_{Na} responses to a pseudo-transduction current of +10 pA during the action potential under control (thin line) and adrenaline conditions (thick line) shown in Figure 2C.

By using the ORC model, we can estimate ionic current responses to odor stimuli during the activation of action potentials. Figure 3A shows $I_{Ca,T}$ and I_{Na} responses, when the pseudo-transduction current of 5 pA induced action potentials in the control condition (thin line in Figure 2B). $I_{Ca,T}$ was activated faster (arrow in Figure 3A) than I_{Na} because the activation voltage of $I_{Ca,T}$ in ORCs is more negative than that of I_{Na} (Kawai *et al.*, 1996). When the pseudo-transduction current of 5 pA was injected into the model under the adrenaline condition, neither $I_{Ca,T}$ nor I_{Na} (data not shown) was activated during the membrane potential change (thick line in Figure 2B). With the strong stimulation (10 pA), adrenaline increased the activation frequency of $I_{Ca,T}$ and decreased its amplitude (data not shown). In contrast, adrenaline increased both the activation frequency of I_{Na} and its amplitude (Figure 3B). A similar result was obtained when the only $I_{Ca,T}$ component was removed from the ORC model, suggesting that I_{Na} is responsible for the increase of spike activity by adrenaline (Figure 2C).

Discussion

In the present study, the effects of adrenaline on the action potentials were studied using a computer simulation. The results of the simulated step current injection were almost consistent with those of the previous experiment (Kawai *et al.*, 1999). However, there were slight differences of the mean slope in the stimulus–response relation between the simulation (Figure 1C) and the previous experiment [figure 1C in (Kawai *et al.*, 1999)]. Adrenaline made the mean slope in the experiment slightly steeper than that in the simulation. The reasons for these differences are unclear. Recently, it has been shown that dopamine modulates a K^+ current in rat ORCs via cAMP (Vargas and Lucero, 1999). Since a β-adrenergic receptor uses cAMP as a second messenger, adrenaline might also modulate K^+ currents in newt ORCs and change their spike activities.

Adrenaline may regulate vasomotor tone and secretion from the Bowman's glands, which modulate odorant access to and clearance from the olfactory epithelium (Getchell and Getchell, 1984; Zielinski *et al.*, 1989; Chen *et al.*, 1993). Although the present simulation does not exclude this possibility, the modulation by adrenaline of spiking activities should be regarded as an important effect of adrenaline. A 3-fold increase in the slope of the simulated intensity–response relation for odor stimuli (Figure 2D) seems to be quite significant. Consequently, ORCs can encode the difference between the presence of an odor stimulus and its absence, since the amplitude of the transduction current rises with the increase of odor concentration (Firestein *et al.*, 1993). Under natural conditions this may contribute to improving the identification ability for the presence of odorants.

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