Group 2-2

A possible role of Ih modulation by a group III metabotropic glutamate receptor on the activity of rods in the newt retina

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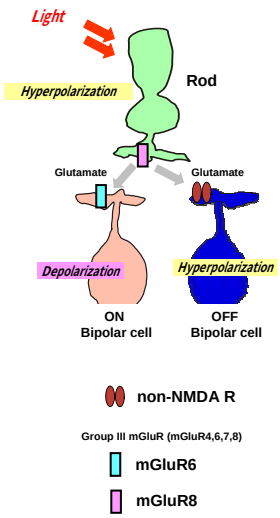
① Introduction

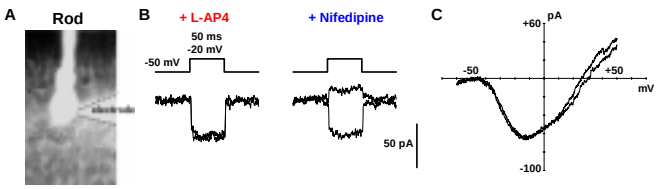


ON and OFF bipolar cells (BCs) receive glutamatergic inputs from photoreceptors via a subtype of group **III** metabotropic glutamate receptors (mGluR6), and ionotropic glutamate receptors (non-NMDA R), respectively. It has been reported that another group **III** mGluR (mGluR8) is located at the terminal of rat photoreceptors. We found that a group **III** mGluR selective agonist L-AP4 not only abolished photoresponses of ON BCs but also reduced those of OFF BCs in the newt retina, and that L-AP4 did not affect the glutamate-induced responses in OFF BCs.

To understand the mechanism how photo-responses of OFF BCs were reduced by the activation of mGluRs, the effects of L-AP4 on the membrane currents of rods were examined in the newt retinal slice preparation. L-AP4 did not influence the Ca current (ICa) but suppressed the hyperpolarization-activated current (Ih) by shifting the activation curve to a negative potential. A possible role of Ih modulation was evaluated by using a modified mathematical model of rods constructed by Kamiyama et al. (1996).

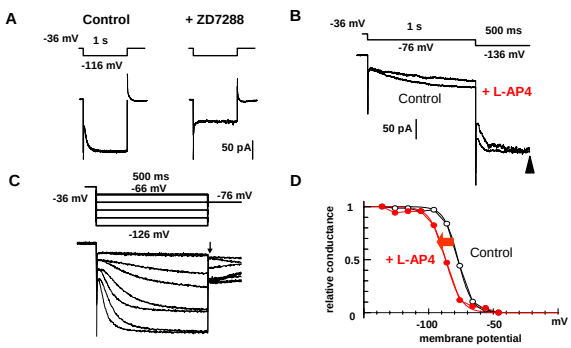
② Experiments

②-1 No effect of L-AP4 on ICa



A) A rod intracellularly stained with Lucifer yellow.
B) ICa (*left*, thin) evoked by a depolarizing pulse. L-AP4 (200 μM) did not affect ICa (*left*, thick). ICa was identified as L-type because Nifedipine (10 μM) abolished ICa (*right*, thick).
C) ICa-V relationship in the absence (thin line) and presence (thick line) of L-AP4. L-AP4 showed no significant effect.

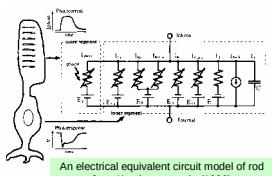
②-2 Suppressive effect of L-AP4 on Ih



A) A hyperpolarizing voltage pulse elicited a slowly developing inward current, which was diminished by a specific blocker of Ih, ZD 7288 (100 μM).
B) L-AP4 (200 μM; thick line) slowed down the activation kinetics of Ih but did not affect the maximal current amplitude evoked by strong hyperpolarization (arrow head).
C) The activation curve of Ih was obtained by measuring the tail currents evoked by a series of conditioning pulses in the absence (thin line) and presence (thick line) of L-AP4.
D) A negative shift of the activation curve by L-AP4.

③ Model simulation

③-1 Mathematical model of rod



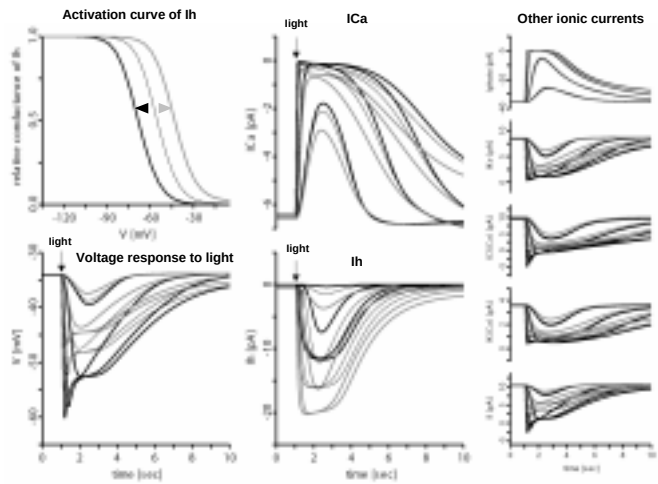
An electrical equivalent circuit model of rod from Kamiyama et al., (1996)

The mathematical model of rod constructed by Kamiyama et al. (1996) was downloaded from ***NRV Platform***.

To estimate a possible role of Ih modulation by L-AP4 on the activity of rods quantitatively, the activation curve of Ih in the model was shifted by ±15 mV. Voltage responses and ionic currents evoked by a flash light were simulated. Among various ionic currents we focused on the effect of Ih modulation on ICa, which is essential for transmitter release.

The model downloaded from *NRV Platform*

③-2 Changes simulated by shifting the activation curve of Ih



The electrical responses of the model rod to a 50ms light flash (arrow) were simulated. Stimulus intensities were 0.03, 0.3, 3.0, 30.0 Rh* sec^{-1}.

When the activation curve of Ih was shifted by –15 mV (*top left*, thick line), Ih became smaller in amplitude (*bottom center*, thick line) and voltage responses to bright stimuli became larger (*bottom left*, thick line) than the control (thin line). Reactivation of ICa became slow slightly. These changes may reduce the transmitter release during photoresponses, and slow down the recovery of transmitter release in the dark.

When the activation curve of Ih was shifted by +15 mV (top left, gray line), Ih became larger (*bottom center*, gray line) and voltage responses to light became smaller and more depolarized than the control (thin line). As a result, ICa was more activated and reactivation of ICa was slightly accelerated. These changes may increase transmitter release during photoresponses, and accelerate the recovery of transmitter release in the dark.

④ Discussion

In the newt retina L-AP4 did not affect ICa of rods but inhibited Ih by shifting the activation curve of Ih to a negative potential.

The simulation study suggests that the shift of activation curve of Ih can change the reactivation kinetics of ICa. It is likely that such changes may modulate the transmitter release from rods and influence the temporal properties of synaptic transmission to second-order neurons.

Since the parameters of the model was not obtained from the newt rod, it is necessary to construct a model of the newt rod for simulation and to examine experimentally the transfer function by simultaneous recordings from rod and OFF bipolar cell.