The Role of Gap Junction in the Goldfish's Motion Detection Measured with Optomotor Response

Young-Sub Lee, Young-Hyun Yoon, Chang-Sub Jung

Physics and Biophysics Section, Department of Natural Sciences, College of Medicine, The Catholic University of Korea, Seoul, Korea

Gap junctions are distributed within various cells and function as electrical synapses by freely exchanging small molecules. In the retina, the practical role of gap junctions in an animal's motion detection has not been investigated very much. In this study, optomotor response (OMR) was used to investigate the effects of drugs which modulate electrical synapses between retinal cells. An injection of carbenoxolone, 8-Br-cAMP, sodium nitroprusside (SNP) or 8-Br-cGMP decreased goldfish's OMR in both light and dark conditions. In light conditions, an intravitreal injection of dopamine, SKF-38393 or eticlopride decreased OMR and that of SCH-23390 increased it. In dark conditions, the injections produced opposite results: dopamine, SKF-38393 and eticlopride increased OMR and SCH-23390 caused OMR to decrease. These results indicate that gap junctions between retinal cells have an important role in goldfish's motion detection.

Key Words: Motion detection, Gap junction, Horizontal cell, Dopamine, Nitric oxide

INTRODUCTION

A gap junction is an intercellular channel, which is composed of two connexons from each adjacent cell. It functions as an electrical synapse, through which molecules smaller than 1.2 kD can freely pass. Gap junctions are known to be well-developed between cardiac muscle cells where they induce synchronous contraction of cardiac muscles, and between neurons of a nervous system. In a fish retina, gap junctions are known to be localized in horizontal cell (HC) bodies, HC axon terminals, amacrine cells, photoreceptors, bipolar cells and interplexiform cells.[1-5] Among these, gap junctions between HCs have been most investigated. It was reported that electrical coupling between HCs *in vitro* can be altered by dopamine, cyclic AMP, cyclic GMP, nitric oxide and alteration of pH.[4,6,7] However, what would be the influence of altering gap-junctional coupling between retinal cells on an animal's motion detection has not been studied.

Optomotor response (OMR) - in which an animal follows an object around with its eyes, head or body - is one of the behavioral tests used to quantitatively investigate motion detection. Through OMR, it was discovered that motion detection in goldfish is "color blind", and that the blockade of D_2-dopamine receptor, nicotinic acetylcholine receptor (nAChR) or GABAa receptor impairs goldfish's motion.[8-10] In this study, the effect of altering of electrical coupling on goldfish's motion detection was investigated by measuring OMR change after intravitreally injecting specific drugs. Carbenoxolone was used as a direct gap junction blocker, and dopamine, sodium nitroprusside (SNP) and their related drugs were used as indirect gap junction mediators. Overall, this study was undertaken to show the influence of gap junctions on motion detection, the cell types which mainly contribute to the influence, and correlation between the substances that induce changes of electrical coupling through OMR.

MATERIALS AND METHODS

1. Animals

Goldfish (*Carassius auratus*) used in our experiment were

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Corresponding Author: Chang-Sub Jung, Physics and Biophysics Section, Department of Natural Sciences, College of Medicine, The Catholic University of Korea, 505, Banpo-dong, Seocho-gu, Seoul 137-701, Korea.
Tel: 02)590-1257, Fax: 02)535-1270
E-mail: cjung@catholic.ac.kr

obtained at an expert fish store and kept under a 12-hour light/dark cycle in large tanks. Body length ranged from 7 to 9 cm, and body weight ranged from 10 to 16 g.

2. Experimental setup and light intensities

Experimental setup (Fig. 1) was similar to ones used by Schaerer and Neumeyer.[8] A columnar glass fishbowl (12 cm diameter) containing an animal was placed in the white/deep-blue (wavelength λ=441 nm) stripe pattern cylinder (15 cm diameter and 3.8 cm width of each stripe). The pattern cylinder was rotated at four different velocities [revolutions per minute (rpm) of the pattern cylinder]: 6, 8, 10 and 12 rpm. The light source was an LCD projector (XG-SV1A, Sharp, Japan), and the light intensity was controlled by a pair of polarizing plates (Kent, Japan). In dark conditions, the openable shutter was placed in front of LCD projector to prevent the light from illuminating the fishbowl during periods when the pattern cylinder was not rotating. In order to make the inside of the fishbowl dark and then to prevent the animal's mirror image from forming, the cover, which was made with a black urethane sponge and fit to the size of the fishbowl, was placed on top. To prevent an external light from entering the setup, it was veiled with double black curtains.

The light intensities were measured with a radiometer (IL1400A, International Light, Newburyport, MA). For deep-blue stripes of the pattern cylinder, the light intensity measured in light conditions was 133 nW/cm^2 (3.01×10^{11} photons/cm^2 · s) and that measured in dark conditions was 9.3 nW/cm^2 (2.11×10^{10} photons/cm^2 · s). The goldfish and pattern movement were recorded by a miniature camera (SK-2005X, Huviron Co., LTD, Gyeonggi-do, Korea), which was set up under the fishbowl and observed with the line- connected computer system.

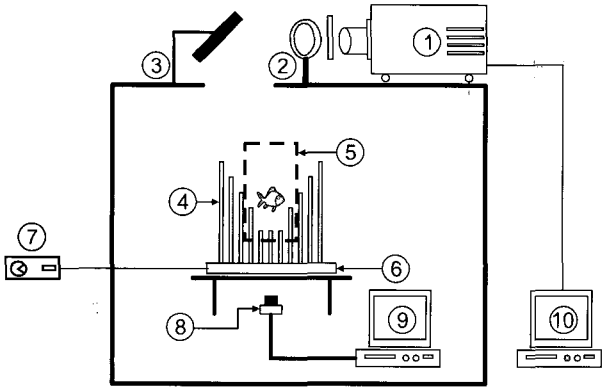

Fig. 1. The diagram of device for optomotor response measurements. ① LCD projector, ② polarizing plates and shutter, ③ mirror, ④ striped pattern cylinder, ⑤ columnar glass fishbowl, ⑥ disk rotated by motor, ⑦ disk controller, ⑧ miniature camera, ⑨ recording computer, ⑩ output signal computer.

3. Measurement of optomotor response

Measurement of optomotor response was similar to the method described by Schaerer and Neumeyer.[8] An animal to be tested was placed in a fishbowl and transferred into the setup during the day. In cases of experiments in dark conditions, about 1 hour of adaptation with no illumination was given to the animal before the control OMR measurement. The control OMR measurement was performed 6 times at given pattern velocities. Each measurement consisted of a 1-min period of pattern rotation and a subsequent 0.5-min period without pattern movement. The pattern cylinder was rotated clockwise and counterclockwise alternately to prevent the directional adaptation of a goldfish. The order of measurements was chosen in a way that OMRs were measured from the slowest to the fastest pattern velocity, and measurements were recorded at 6 identical intervals at each pattern velocity. The same method was used for the drug injection (or vehicle injection) and recovery OMR measurements.

4. Drugs and injections

Carbenoxolone (direct gap junction blocker), 8-Br-cAMP (PKA activator), dopamine and its related drugs [SCH-23390 (D_1-R antagonist), SKF-38393 (D_1-R agonist) and eticlopride (D_2-R antagonist)], sodium nitroprusside (SNP; nitric oxide donor), and 8-Br-cGMP (PKG activator) were injected into goldfish by intravitreal injection. Before performing the drug injection experiment, vehicle injection experiments, in which only Ringer's solution (pH 7.40, in mM: 125 NaCl, 2.6 KCl, 2.5 $CaCl_2$, 1 $MgCl_2$, 10 glucose and 10 HEPES) used as a solvent, were performed on 10 animals to investigate influences of anesthesia and Ringer's solution on goldfish's motion detection. All drugs except for 8-Br-cAMP were dissolved in Ringer's solution. Because of the problem of solubility, 8-Br-cAMP was first dissolved in dimethyl sulfoxide (DMSO) to 2 mM, and

was then diluted with Ringer's solution to 20 μM.

All drugs were dissolved and 2.0 μl was injected into goldfish by intravitreal injection. The Drugs are thought to have been diluted in the eyecups about 0.05 times, because the mean eyecup volume calculated from our dimensional measurement was about 40 μl. Anesthesia was similar to that used by Senut et al.[11] After the animal had been anesthetized for 5 min in ice, drugs were injected intraocularly by Hamilton syringe (701RN, Hamilton Co., Reno, Nevada). In dark conditions, anesthesia and injection were performed in a darkroom which was only illuminated by dim light. After an injection, the animal was transferred into the setup and adapted to it for 15~20 min. Then, the drug injection OMR was measured.

Behavioral and drug injection experiments were performed according to guidelines for the use of fish in research, established by American Fisheries Society (AFS).

5. Data acquisition, data treatment and statistics

The method described by Mora-Ferrer and Gangluff was consulted for data acquisition and treatment.[9] Data were obtained by subtracting rounds fish swam against the direction of the pattern movement from rounds fish swam with the direction of the pattern movement, based on the direction of goldfish's head. The mean value of 6 measurement values which were obtained from one animal at each pattern velocity was used for a data treatment. In this way, mean OMR values of a total of 5 animals in which the recovery OMRs returned to the control OMR level were obtained and averaged in each condition of each drug. In order to deduce a general tendency, which is unrelated to the pattern velocity, the mean data were given in percent of the pattern velocities used for their measurements [OMR=(mean rotation number per minute/ pattern velocity)×100 (%)]. Even all measurements were performed at 4 different pattern velocities, there were no significant results between the pattern velocities. Therefore data measured at 12 rpm pattern velocity will be shown in a diagram form excepting the data of vehicle and carbenoxolone.

In all plots, the data are shown with their respective standard error of the mean (SEM). For statistical comparison, a two-sided paired t-test was used.

RESULTS

Experimental data are presented by comparing averaged data for animals to which drugs were injected in light conditions with those for animals to which the same drugs were injected in dark conditions.

1. Vehicle injection

Because non-injected goldfish were chosen as the controls, vehicle injection was preferentially performed. The control,

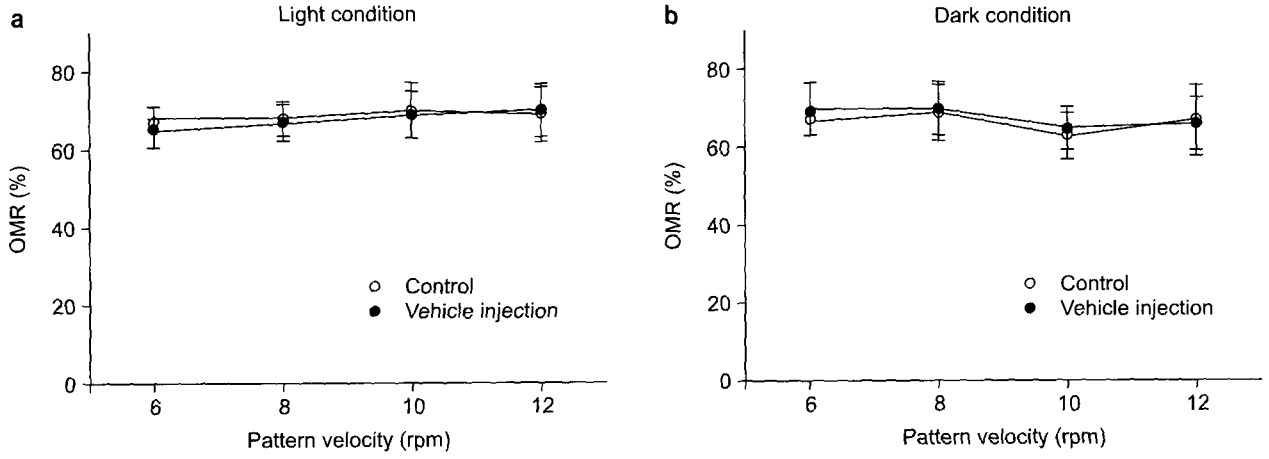

Fig. 2. Averaged optomotor responses of vehicle injection in light (a) and dark conditions (b). (a) In light conditions, vehicle injection (n=5) induced no significant OMR change for all pattern velocities ($P \geq 0.05$). (b) In dark conditions, vehicle injection (n=5) induced no significant OMR change for all pattern velocities ($P \geq 0.05$). x axis: pattern velocity [revolutions per minute (rpm)]; y axis: averaged OMR (%); error bars: SEM.

vehicle injection and recovery OMRs are shown in Fig. 2. In light conditions, the control and vehicle injection OMRs varied little (Fig. 2a), and the changes were insignificant for all pattern velocities ($P \geq 0.16$). Similarly, in dark conditions, the control and vehicle injection OMRs varied little (Fig. 2b), and the changes were insignificant for all pattern velocities ($P \geq 0.266$).

2. 1 mM carbenoxolone

Carbenoxolone was used as a direct gap junction blocker.[12] Control, drug injection and recovery OMRs of 1 mM carbenoxolone are shown in Fig. 3. In light conditions, the drug injection OMR decreased by 36.5~53.2% at four different pattern velocities, compared with the control OMR (Fig. 3a), and the changes were highly significant for all pattern velocities ($P \leq 0.008$). In dark conditions, the drug injection OMR decreased by 26.1~48.9%, compared with the control OMR (Fig. 3b), and the changes were significant for all pattern velocities ($P \leq 0.023$).

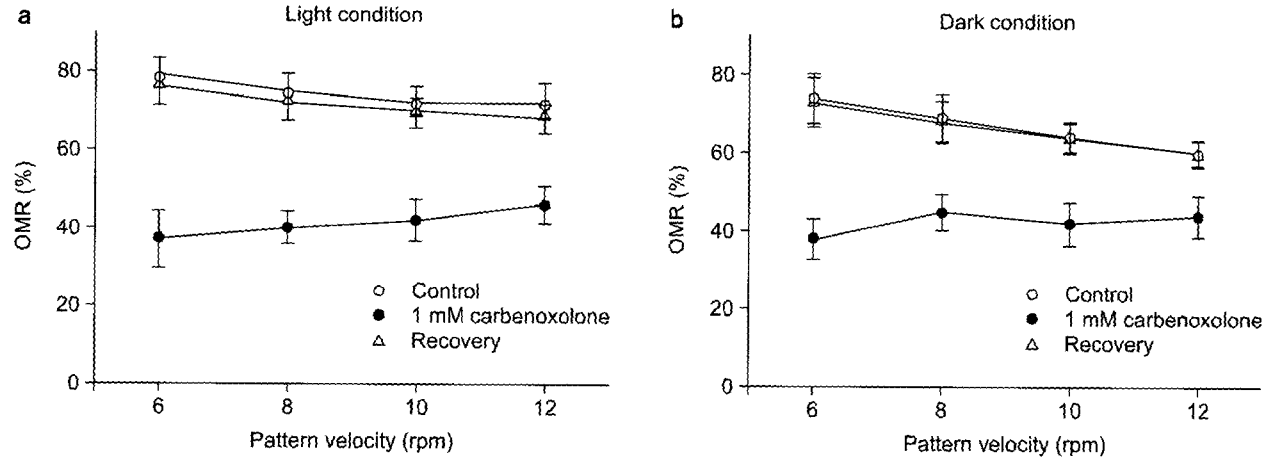

Fig. 3. Averaged optomotor responses of 1 mM carbenoxolone in light (a) and dark conditions (b). (a) In light conditions, an injection of carbenoxolone (n=5) induced about 35~50% decreases of OMR for all pattern velocities highly significantly ($P \leq 0.01$). (b) In dark conditions, an injection of carbenoxolone (n=5) induced about 25~50% decreases of OMR for all pattern velocities significantly ($P \leq 0.05$). x axis: pattern velocity [revolutions per minute (rpm)]; y axis: averaged OMR (%); error bars: SEM.

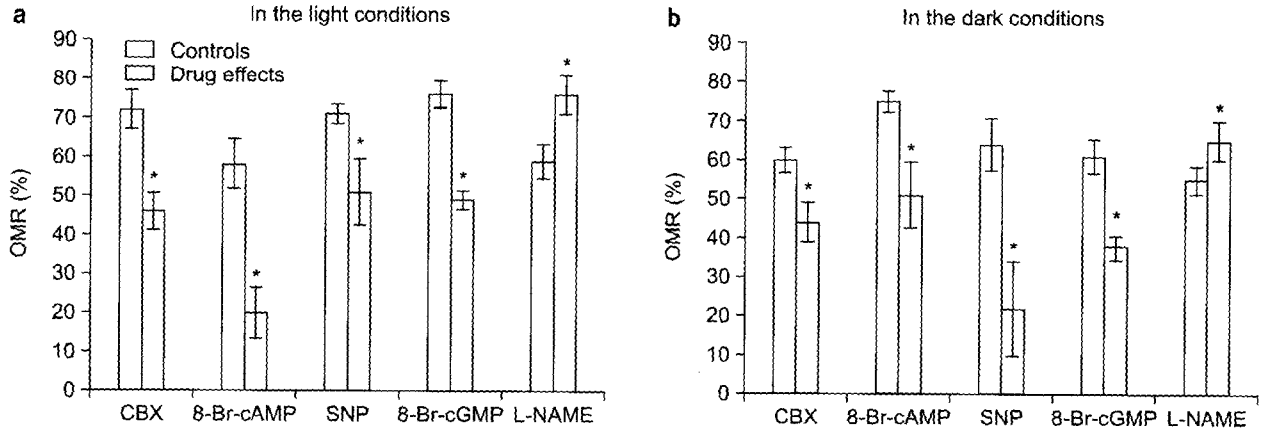

Fig. 4. Averaged optomotor responses of gap-junction blockers and nitric oxide related agents in the light (a) and dark (b) conditions. (a) Gap-junction blocker related agents carbenoxolone (1 mM, CBX), 8-Br-cAMP (20 μM), SNP (1 mM), and 8-Br-cGMP (200 μM), while nitric oxide synthase inhibitor L-NAME (1 mM) increased the OMR in the light conditions. (b) The effects on the OMR by the same drugs were almost same effects in the dark conditions In all figures, asterisks (*) indicate a significant difference from controls ($P < 0.05$; Student's t test). Error bars indicate SEM.

3. Effects of nitric oxide and its related drugs on OMR at 12 rpm pattern velocity

Optomotor responses of gap-junction blockers and nitric oxide related agents were measured in the light and dark conditions (Fig. 4). 8-Br-cAMP, which is analogous to cAMP, is known as a gap junction blocker through protein kinase A (PKA).[6,7] In light conditions, 20 μM 8-Br-cAMP injection OMR greatly decreased by 65.5%, compared with the control OMR. Similarly, in dark conditions, 8-Br-cAMP injection OMR decreased by 32.0%. Nitric oxide is also known to cause a gap junction blockade. SNP was used as a nitric oxide donor.[7,13] SNP (1 mM) injection OMR decreased by 28.2% in light conditions and dramatically decreased by 65.6% in dark conditions, compared with the control OMRs respectively. 8-Br-cGMP, which is analogous to cGMP, is related to nitric oxide and known as a gap junction blocker through protein kinase G (PKG).[7] 8-Br-cGMP (200 μM) injection OMR decreased by 35.6% and 37.7% respectively compared with the control OMRs in both conditions. To investigate whether NOS (nitric oxide synthase) is involved in the action of NO, NOS blocker 1 mM L-NAME injection OMR was measured.[14] In light conditions, 1 mM L-NAME injection OMR increased by 28.8%, compared with the control OMR. In dark conditions, 1 mM L-NAME injection OMR also increased by 18.2%.

4. Dopamine and its related agents at 12 rpm pattern velocity

Optomotor responses of dopamine and its related agents were measured in the light and dark conditions (Fig. 5). Dopamine, which is taken in by dopamine receptors such as D_1-receptor (D_1-R) and D_2-receptor (D_2-R), is known to cause a gap junction blockade when it is received by D_1-R of cone-HC.[6] In light conditions, 20 μM dopamine injection OMR greatly decreased by 59.3%, compared with the control OMR. In contrast, in dark conditions, 20 μM dopamine injection OMR increased by 8.1%. SKF-38393 was used as a D_1-R agonist. SKF38393 (60 μM) injection OMR decreased by 21.9% in light conditions, but increased by 25.9% in dark conditions, compared with the control OMRs. SCH23390 was used as a D_1-R antagonist. SCH23390 (20 μM) injection OMR slightly increased by 8.3% in light conditions, but decreased by 48.8% in dark conditions, compared with the control OMRs. Eticlopride was used as D_2-R antagonist. In light conditions, 50 μM eticlopride injection OMR decreased by 29.3%, compared with the control OMR. In contrast, in dark conditions, 50 μM eticlopride injection OMR increased by 15.9%.

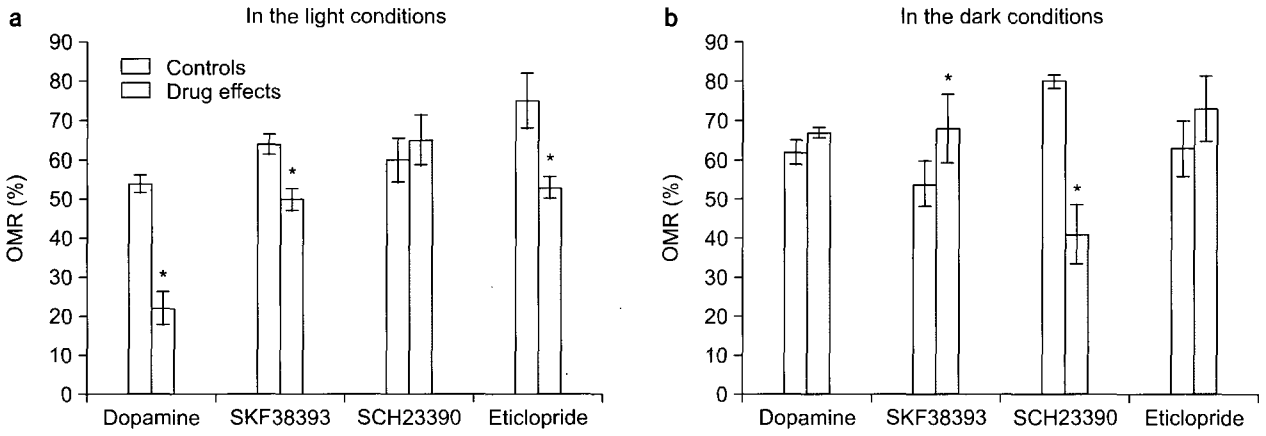

Fig. 5. Averaged optomotor responses of dopamine and its related agents in light (a) and dark (b) conditions. (a) Dopamine (20 μM), a D_1 receptor agonist SKF38393 (60 μM), and D_2 receptor antagonist Eticlopride (50 μM) induced the reduction of the OMR, while SCH23390 (20 μM), a dopamine receptor antagonist, slightly increased the OMR in the dark conditions. (b) In contrast, the effects by the same drugs were opposite effects in the dark conditions. In all figures, asterisks (*) indicate a significant difference from controls ($P<0.05$; Student's t test). Error bars indicate SEM.

DISCUSSION

1. Suitability of stripe color and light intensities

The stripe color of the pattern cylinder used in our experiment was deep blue (λ=441 nm). This was chosen because the light of this wavelength hyperpolarizes the membrane potentials of all three types of cone-HCs as well as rod-HCs in fish. It was reported that null wavelengths for spectral sensitivities of all types of cone-HCs are higher than 500 nm.[15] Therefore, the wavelength with which all types of HCs are hyperpolarized to the same direction would be more suitable to measure the relation between motion detection and gap junction.

The light intensities used in our experiment were 3.01×10^{11} photons/cm^2 · s for light conditions and 2.11×10^{10} photons/cm^2 · s for dark conditions. They were chosen because these light intensities are suitable for deep-blue stripes, compared with the experiment performed by Schaerer and Neumeyer.[8] According to their experiment, for light-adapted state (the wavelength of stripes λ=437 nm), OMR in 3×10^{11} photons/cm^2 · s was about 80% and that in 3×10^{10} photons/cm^2 · s was below 10%. Besides, for dark-adapted state (λ=434 nm), OMR in 2×10^{10} photons/cm^2 · s was above 55%. Therefore, it is highly likely that OMR from 2.11×10^{10} photons/cm^2 · s in our experiment was obtained exactly from dark conditions, but not from light conditions.

2. Effects of gap junction blockers on motion detection

In fish retina, it has been reported that gap junctions are distributed within horizontal cell (HC) bodies, HC axon terminals, amacrine cells, photoreceptors, bipolar cells and interplexiform cells.[1-5] In the present study, the drug injection OMRs of carbenoxolone and 8-Br-cAMP, which are known to block gap junctions, decreased in both light and dark conditions. Because the recovery OMR, measured on the next day, returned to the control OMR level, the changes of goldfish's motion detection were not likely due to ocular damage accompanied during anesthesia or injection procedure. Thus, the above results suggest that gap junctions between retinal cells have an important role in goldfish's motion detection.

In the retina, lateral inhibition was reported to greatly contribute to an animal's motion detection by increasing dark-light contrast.[16] It is known that HCs and amacrine cells participate in the mechanism of lateral inhibition, and that lateral propagation of visual signals in these cells is mediated by gap junctions. Consequently, a blockade of gap junctions is thought to impair an animal's motion detection by decreasing contrast sensitivity. The contrast [Contrast=$(L_{max}-L_{min})/(L_{max}+L_{min})$] between deep-blue and white stripes used in our experiment was 0.123 in light conditions and 0.225 in dark conditions. Thus, even a small loss of contrast sensitivity may have sufficiently impaired goldfish's motion detection.[9]

3. Effects of nitric oxide and its related drugs on motion detection

Nitric oxide is also known to block gap junctions in fish retina by activating soluble guanylate cyclase, which produces cGMP.[7,17] Cyclic GMP is necessary for reversing hyperpolarizing signals of photoreceptors into depolarizing signals of ON-bipolar cells as well as blocking gap junctions.[18] Furthermore, an injection of nitric oxide donor decreases blue/green region sensitivity for light- and dark-adapted goldfish retina.[19] Therefore, our results showing OMR that decreased in both light and dark conditions after an injection of SNP or 8-Br-cGMP are consistent with those studies.

4. Effects of dopamine and its related drugs on motion detection

Dopamine acts on D_1-R of cone-HCs and then causes a gap junction blockade through cAMP (Mangel & Dowling, 1987). Rod-HCs do not seem to have D_1-R, because it was not affected by dopamine.[20,21] Furthermore, rod-HCs have been shown to be not connected to interplexiform cells, which are dopaminergic cells in fish.[20] In interplexiform cells, D_2-R is known to act as an autoreceptor, which modulates the secretion of dopamine through feedback,[20,22] and is distributed to retinal pigment epithelium (RPE) and photoreceptors in fish.[23,24] In studies on receptive field size of HCs, an injection of dopamine (0.5~20 μM), SKF-38393 or 8-Br-cAMP in fish and mammals reduced receptive field size, while an injection of dopamine (0.2 μM), SCH-23390 or D_2-R agonist, LY171555, increased it.[24,25] Dopamine concentration (1 μM) used in our experiments also induced the reduction of OMR indicating the

reduction of receptive field size.

Our present results with dopamine and its related drugs almost agree with those of receptive field size studies. In light conditions, the drug injection OMR of dopamine, SKF-38393 or eticlopride decreased, while that of SCH-23390 increased. In dark conditions, the injections produced opposite results: dopamine, SKF-38393 and eticlopride increased OMR and SCH-23390 caused OMR to decrease. These results support the hypothesis that OMR changes by dopamine and D_1-R related drugs are due to the alteration of gap junctions between HCs, even though there is a report that D_1-R is distributed to many kinds of cells in goldfish retina.[26] The fact that an injection of eticlopride induced the same effect as that of dopamine also supports this hypothesis. The decrease of goldfish's OMR by eticlopride in light conditions might be due to disturbance of dopamine autoreception (which might be linked to an increase of endogenous dopamine), in interplexiform cells.

A question arises then how dopamine affected goldfish's motion detection in dark conditions, even though rod-HCs have no D_1-R. The answer could be explained by cone system effects on rod-system in mixed ON-bipolar cells. Mixed ON-bipolar cells take visual signals from cones as well as rods.[27] When the gap junction conductance between cone-HCs becomes different by dopamine or its related drug, it is thought to affect OMR-related signals of cones. And mixed ON-bipolar cells seem to receive OMR-related signals from cones and rods complementarily. Thus, although gap junctions between rod-HCs were not affected by dopamine, mixed ON-bipolar cells would receive OMR-related signals from rods more strongly (as if rod-HCs had become more electrically coupled when gap junctions between cone-HCs were blocked by dopamine,) which resulted in increased OMR. As shown in the results, the drug injection OMR of 8-Br-cAMP also decreased in dark conditions, suggesting that gap junctions between rod-HCs can be blocked by cAMP which is produced through an unknown mechanism.

The relationship between dopaminergic regulation and the adaptation state of fish retinas is controversial. Mangel and Dowling observed that after leaving goldfish retinas in dark conditions for 100~110 min, amplitudes of responses for stimulation on L-type cone-HCs became similar to the ones which were measured in light conditions after applying dopamine.[6] This means that interplexiform cells can release dopamine when stimulated by dark conditions. In contrast, however, several authors reported that interplexiform cells release dopamine when stimulated by light conditions.[22,28-31] Our present results are largely accordant with Manel and Dowling's observation. The effects of D_1-R related drugs were more prominent in dark conditions, while dopamine and D_2-R antagonist decreased OMR more strongly in light conditions. Therefore, according to the hypothesis of Mangel and Dowling,[6] these results can be explained by the fact that facilitation or blockade of D_1-R is more effective in dark conditions, because enough dopamine has already been released. In addition, exogenous or endogenous dopamine is more effective in light conditions, because the amount of dopamine which has been released is relatively small.

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가톨릭대학교 의과대학 자연과학교실 물리학과

이영섭 · 윤영현 · 정창섭

갭 정션(gap junction)은 다양한 세포에 분포되어 있으며 분자 수준의 작은 물질들이 자유롭게 교환되는 전기적 시냅스다. 망막에서, 갭 정션의 차단이 동물의 동작 감지(motion detection)에 실제적으로 어떤 영향을 주는지에 대해서는 거의 조사되지 않았다. 본 연구에서는, 망막 세포 간의 전기적 시냅스를 조절하는 약물이 금붕어의 동작 감지에 어떠한 영향을 주는지를 조사하기 위해 시각운동 반응(optomotor response, OMR)이 사용되었다. 갭 정션 차단제인 carbenoxolone, 8-bromo cyclic AMP, sodium nitroprusside (SNP), 8-bromo-cyclic GMP 등의 초자체 내 주사는 광- 및 암-상태에서 모두 OMR을 감소시켰다. 광-상태에서 dopamine, SKF-38393 및 eticlopride의 주사는 OMR을 감소시킨 반면 SCH-23390의 주사는 OMR을 증가시켰다. 암-상태에서는 결과가 반대로 나타났다: 즉 dopamine, SKF-38393 및 eticlopride의 주사는 OMR을 증가시킨 반면 SCH-23390의 주사는 OMR을 감소시켰다. 이러한 결과는 망막 세포들 사이의 갭 정션이 금붕어의 동작 감지에 중요한 역할을 담당하고 있음을 시사한다.

중심단어: 동작감지, 갭 정션, 수평세포, 도파민, 산화질소