

## Electrically-evoked Neural Activities of *rd1* Mice Retinal Ganglion Cells by Repetitive Pulse Stimulation

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For successful visual perception by visual prosthesis using electrical stimulation, it is essential to develop an effective stimulation strategy based on understanding of retinal ganglion cell (RGC) responses to electrical stimulation. We studied RGC responses to repetitive electrical stimulation pulses to develop a stimulation strategy using stimulation pulse frequency modulation. Retinal patches of photoreceptor-degenerated retinas from *rd1* mice were attached to a planar multi-electrode array (MEA) and RGC spike trains responding to electrical stimulation pulse trains with various pulse frequencies were observed. RGC responses were strongly dependent on inter-pulse interval when it was varied from 500 to 10 ms. Although the evoked spikes were suppressed with increasing pulse rate, the number of evoked spikes were >60% of the maximal responses when the inter-pulse intervals exceeded 100 ms. Based on this, we investigated the modulation of evoked RGC firing rates while increasing the pulse frequency from 1 to 10 pulses per second (or Hz) to deduce the optimal pulse frequency range for modulation of RGC response strength. RGC response strength monotonically and linearly increased within the stimulation frequency of 1~9 Hz. The results suggest that the evoked neural activities of RGCs in degenerated retina can be reliably controlled by pulse frequency modulation, and may be used as a stimulation strategy for visual neural prosthesis.

**Key Words:** Degenerated retina, Microelectrode array (MEA), Retinal ganglion cells, Retinal implant, Electrical stimulation, Visual neural prosthesis

### INTRODUCTION

Visual neural prostheses such as retinal implant are electrical stimulation devices designed to restore visual function of totally-blind patients due to degenerative retinal diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) (Zrenner, 2002; Merabet et al., 2005). Various efforts toward implementation of visual prosthetic device have involved development of suitable electrodes, circuitry, packaging, and surgical implantation techniques (Hesse et al., 2000; Kazemi et al., 2004; Seo et al., 2004; Sivaprakasam et al., 2005).

Visual information should be transmitted to the brain by electrical stimulation. Perception of simple visual patterns or phosphenes have been reported from clinical trials of human blind patients (Veraart et al., 1998; Humayun et al., 1999; Humayun et al., 2003; Rizzo et al., 2003; Hornig et al., 2005). Based on an in-vitro model of retinal implant that consists of retinal patches mounted on a planar multi-electrode array (MEA), several studies on the properties of electrically-evoked firing of retinal ganglion cells (RGCs)

have increased the basic knowledge required to determine effective methods of visual stimulation (Stett et al., 2000; Jensen and Rizzo, 2007; Ryu et al., 2009b). Recently, we showed that RGC response strength can be effectively controlled by amplitude modulation of stimulation pulse trains so that light intensity variation can be encoded within the RGC spike trains (Ryu et al., 2009b). Fried et al. (2006) showed that the natural pattern of RGC spike trains responding to light can be replicated by electrical stimulation.

Most of the concerned studies have been performed using normal retina patches. However, the ultimate targets of visual prosthesis are blind patients whose retinal networks are significantly altered due to the degeneration of the photoreceptors. Thus neurophysiological studies on the electrically-evoked RGC responses from degenerated retina are required. Several recent studies using *rd1* mouse model of retinitis pigmentosa (RP) have reported that neurophysiological characteristics of RGCs are significantly changed in degenerated retinas (Ye and Goo, 2007; Margolis et al., 2008; Stasheff, 2008). Rhythmic oscillation with a frequency of approximately 10 Hz was observed from field potential recordings from *rd1* retinas (Ye and Goo, 2007; Margolis et al., 2008). It was also observed that both spontaneous and electrically-evoked RGC spike firing show rhythmic bursting patterns with a frequency of approx-

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**ABBREVIATIONS:** RGC, retinal ganglion cell; MEA, multi-electrode array.

imately 10 Hz (Stasheff, 2008; Ryu et al., 2009a). In spite of this, it seems feasible that RGC response strength could be efficiently controlled by pulse amplitude modulation for the *rd1* retina (Ryu et al., 2009a).

In this study, we investigated whether pulse frequency modulation could be used as a stimulation strategy for visual neural prosthesis. Changes in neural activities responding to repetitive stimulation by pulse trains applied with various inter-pulse intervals were observed. The results showed that the response strength of the RGCs of *rd1* mice could be effectively modulated by inter-pulse interval, and, thus, by pulse frequency, as previously shown for normal retina (Jensen and Rizzo, 2007). An optimal range for the pulse frequency modulation was presently determined by observing the frequency ranges where the RGC response strength was increased monotonically by pulse frequency.

## METHODS

### Retinal tissue preparation

Animal use protocols were approved by the institutional animal care committee of Chungbuk National University. *Rd1* mice (C3H/HeJ strain) were used as the animal model of retinal degeneration. The retinal patches were prepared as previously described (Stett et al., 2000). The animals were anesthetized with intramuscular injections of Zoletin 50 (zolazepam hydroxide, 125 mg/5 ml) and Rumpun (xylazine hydroxide, 23.32 mg/ml) sufficient to extinguish the forefoot withdrawal reflex. The eyeball was enucleated and the retina was isolated and cut to retinal patches of approximately 3×3 mm. The retinal patches were placed in artificial cerebrospinal fluid (ACSF) comprised of 124 mM NaCl, 10 mM glucose, 1.15 mM  $\text{KH}_2\text{PO}_4$ , 25 mM  $\text{NaHCO}_3$ , 1.15 mM  $\text{MgSO}_4$ , 2.5 mM  $\text{CaCl}_2$ , and 5 mM KCl, bubbled with 95%  $\text{O}_2$  and 5%  $\text{CO}_2$  with pH of 7.3~7.4 at 32°C, and then mounted onto a planar MEA. The retinal patches were placed ganglion cell layer down onto the MEA.

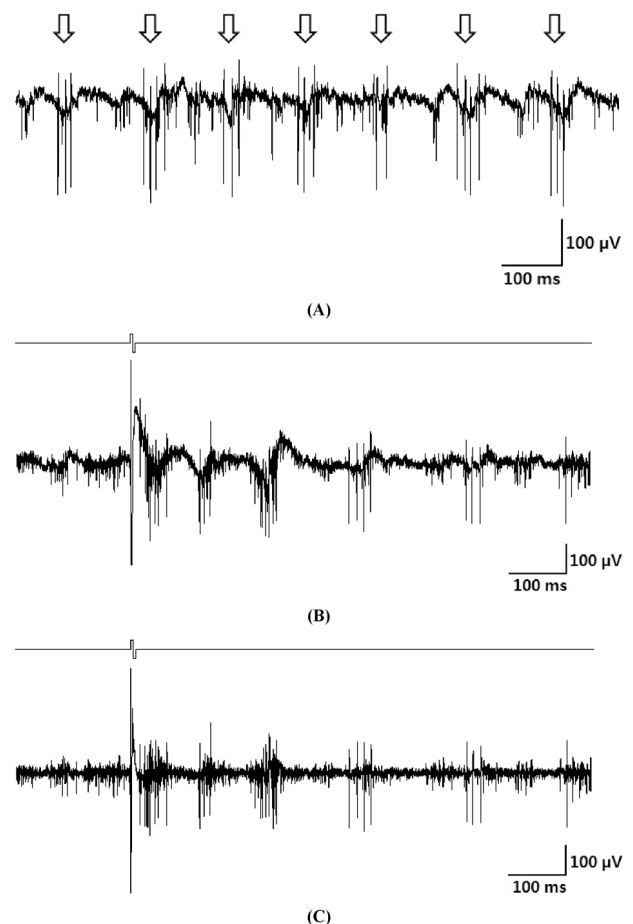
### Multi-electrode array and data recording

A planar MEA containing 64 TiN electrodes (circular shape, diameters: 30  $\mu\text{m}$ ) on a glass substrate in an 8×8 square-type grid layout (Multichannel Systems GmbH, Germany) was used for the recording of field potential and spiking activities from RGCs. Four electrodes at the vertices were inactive. The inter-electrode spacings were 200  $\mu\text{m}$ . Impedances of the electrodes were approximately 50 k $\Omega$  at 1 kHz. The MEA60 data acquisition system (Multichannel Systems) consisted of a RS-232 interface, an integrated 60-channel preamplifier and MEA 1060 bandpass filter (amplification gain: 1,200, passband: 10~3,000 Hz), and a personal computer. The waveforms were recorded with a sampling rate of 25 kHz/channel. Raw recorded data were stored on a hard disk. As activities of more than one RGC can be recorded in one channel of the MEA, a procedure to sort multi-unit activities to single-unit activity was also carried out.

### Electrical stimulation

Charge-balanced biphasic current pulse trains were generated (anodic pulse first, no temporal separation between two phases). Pulse amplitude and duration were fixed at

30  $\mu\text{A}$  and 500  $\mu\text{s}$ , respectively, which can reliably evoke RGC response (Ryu et al., 2009a). Stimulation pulses were generated by a STG 1004 stimulus generator (Multichannel Systems) and applied from a single electrode at the center of the MEA, with RGC responses being recorded from other channels. Electrical stimulations were performed in three sessions to observe response characteristics of RGCs for different inter-pulse intervals and, thus, different pulse frequencies. First, paired-pulse stimulations were applied while the inter-pulse intervals were varied from 500~10 ms (500, 400, 300, 200, 100, 90, 70, 50, 30, 10 ms) and intervals between pulse pairs were fixed at 2 s. Each trial of 10 pulse pairs was repeated 10 times. Second, five pulses were repeatedly applied with inter-pulse intervals of 500~10 ms. Interval between five pulse groups were fixed to 2 s. Third, a session was prepared to obtain the response curves of RGC firing rate as a function of stimulation frequency. The pulse frequency was varied from 1~10 Hz by increasing the number of pulses applied within 1 s from 1~10. The intervals between each pulse group with same pulse frequency were 2 s.



**Fig. 1.** (A) A typical raw waveform of spontaneous retinal activity. Rhythmic oscillatory behavior with ~10 Hz frequency is clearly observable from the background. (B) A typical raw waveform recorded under stimulation. (C) Electrically-evoked RGC spike waveforms derived from the raw recording in (B) by highpass filtering (second order Butterworth filter, cutoff frequency: 100 Hz).

## RESULTS

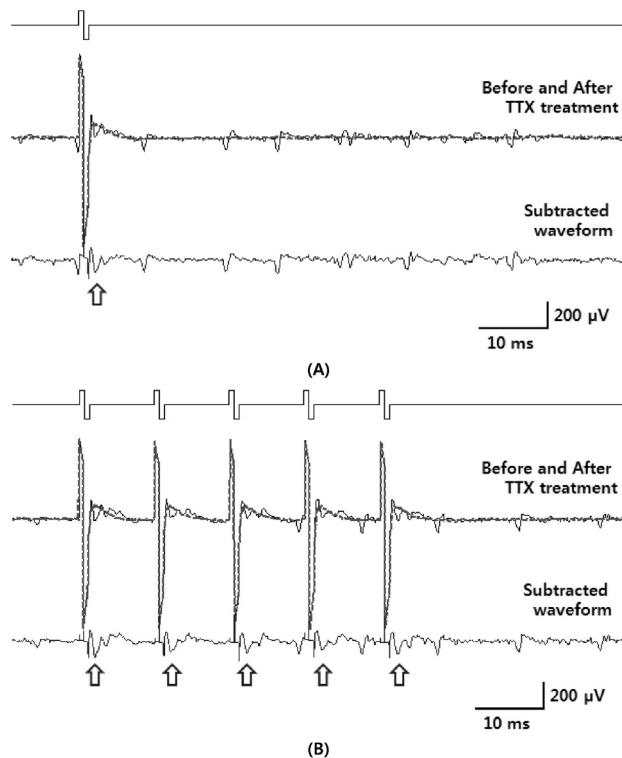
### Characteristics of RGC activities

Single unit spiking activities were found from 374 RGCs of eight retinal patches obtained from eight mice. The average number of single-unit RGCs per patch was  $46.75 \pm 4.39$ . 92 RGCs ( $11.5 \pm 4.03$  RGCs per patch) among these were evoked consistently by stimulation and analyzed. Other RGCs were excluded from further analysis; 38 cells showed irregular evoked firing pattern, 230 RGCs did not show any reliable evoked responses although they showed spontaneous firings, and 14 RGCs could not be clearly sorted from multi-unit recordings.

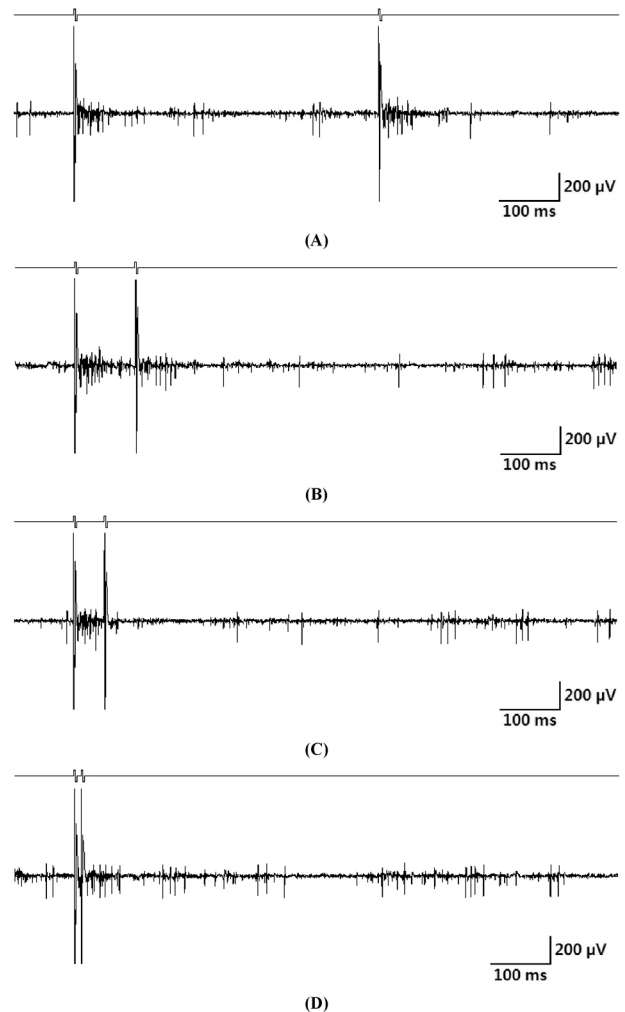
The raw waveforms of spontaneous activities are shown in Fig. 1A. Rhythmic oscillatory behavior with approximately 10 Hz frequency is clearly observed. Along with this, rhythmic bursting of spikes with approximately 10 Hz was visible from the temporal structure of waveforms (Fig. 1A, arrows). A typical raw waveform recorded under stimulation is shown in Fig. 1B. Overall, the waveform was similar in appearance to the spontaneous waveform depicted in Fig. 1A, as both displayed a background oscillatory rhythm and rhythmic bursting type firing of action potentials. However, the number of spikes increased most noticeably within about 100 ms post-stimulus. Two types of evoked RGC spikes were observed as previously reported (Jensen et al., 2005). Long-latency spikes were evoked approximately 20–100 ms after stimulation, and could be clearly identified with-

out contamination from a stimulation artifact. These spikes are regarded as resulting from indirect stimulation of RGCs through the retinal neural network (Jensen et al., 2005). The spike waveforms in Fig. 1C, which were derived from the raw waveform in Fig. 1B, more closely were evident as rhythmic bursting of firing with a frequency of approximately 10 Hz, corresponding to the frequency of spontaneous rhythmic oscillation of field potential in the *rd1* retina (Ryu et al., 2009a).

Another type of response, a short-latency spike, was found to be evoked 2–3 ms after stimulation (Fig. 2). The waveforms of short-latency spikes were significantly contaminated by the stimulation artifact due to the short latency. We used the template subtraction method for the elimination of a stimulation artifact (Fried et al., 2006; Sekirnjak et al., 2006). Templates of artifact waveforms were obtained by suppressing the action potential by the sodium channel blocker tetrodotoxin (TTX, 100 pM). After subtracting the templates from recordings, the short-latency spikes could be clearly recovered (Fig. 2). Short-latency responses can



**Fig. 2.** Short-latency RGC spikes. (A) Inter-pulse interval: 500 ms, (B) inter-pulse interval: 10 ms (Thin solid line: before TTX treatment. Thick dotted line: after TTX treatment. Template subtraction result: indicated by arrows.).



**Fig. 3.** Electrically-evoked RGC responses when a pair of pulses was applied. (A) Inter-pulse interval: 500 ms. (B) Inter-pulse interval: 100 ms. (C) Inter-pulse interval: 50 ms. (D) Inter-pulse interval: 10 ms.

be evoked reliably under high pulse frequencies up to 200 Hz (Fried et al., 2006; Sekirnjak et al., 2006). Only one short-latency spikes were evoked by a single pulse, along with later long-latency spikes.

#### Pulse frequency modulation of RGC response

To characterize the dependency of RGC responses on inter-pulse intervals (and, thus, pulse frequency), a pair of pulses were applied with various inter-pulse intervals, and the responses evoked by the second pulses in the pairs were observed. RGC responses were evoked reliably, while in-

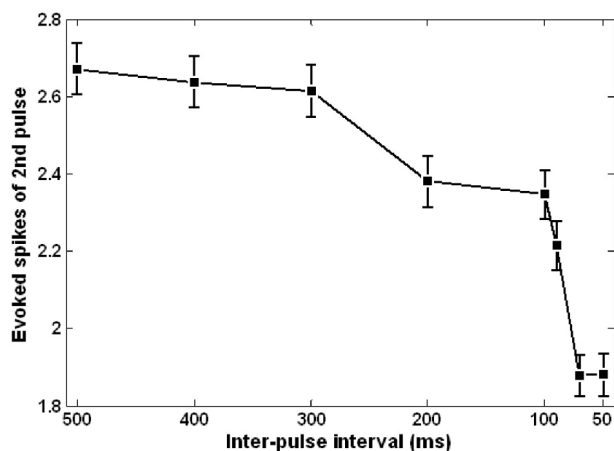


Fig. 4. The number of RGC spikes evoked by second pulses in the pulse pairs plotted as a function of inter-pulse interval (500~50 ms). Each data point was obtained from the average of 75 RGCs. Error bar denotes standard error.

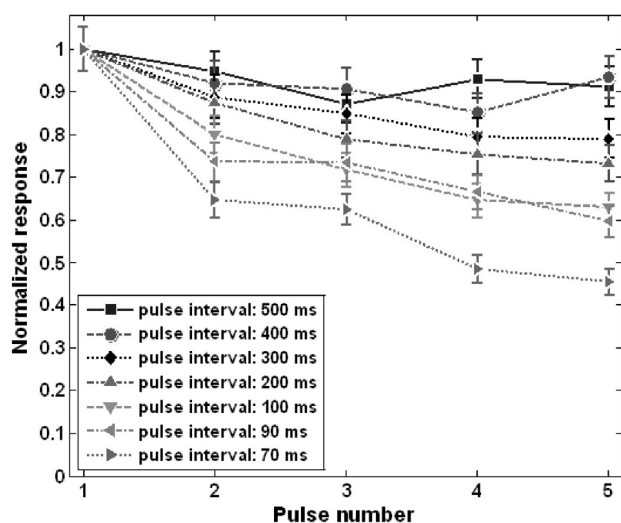


Fig. 5. The RGC response strength (number of spikes normalized to the values for single pulse stimulation) evoked by each pulse of five successive pulses plotted as a function of inter-pulse interval (500~70 ms). The results were obtained from 75 RGCs.

ter-pulse intervals varied from 500 to 100 ms (Fig. 3A, 3B, and 4). The number of evoked spikes began to decrease abruptly when the inter-pulse interval was reduced to 100 ms and was suppressed maximally when the inter-pulse interval was 50 ms (Fig. 3C and 4). When the inter-pulse interval became shorter than 50 ms, the number of spikes evoked by the second pulse appeared again (Fig. 3D).

To ascertain how RGC responses were modulated when more than two pulses were applied, five repetitive pulses of various inter-pulse intervals were applied for the stimulation and the number of spikes evoked by each pulse was counted. The number of evoked response decreased gradually as more stimulation pulses were applied (Fig. 5). In spite of the suppression of evoked responses, 60% of RGC responses still continued to be evoked when the inter-pulse interval was changed from 500 to 100 ms. Similar to the use of paired-pulse stimulation, RGC responses were suppressed drastically when the inter-pulse interval was reduced to <100 ms.

To find an optimal range for the pulse frequency modulation, the number of spikes evoked within 1 s after stimulus onset was plotted as a function of pulse frequency. The response curve shown in Fig. 6 was constructed by increasing the pulse frequency from 1 to 10 Hz (i.e., by decreasing inter-pulse interval). Within the pulse frequency range of 1~9 Hz, the number of spikes increased monotonically and linearly. The spikes evoked by second or later pulses in a pulse train were somewhat suppressed, and this tendency became more pronounced for shorter inter-pulse interval (Fig. 5). However, long-latency RGC responses were still evoked by repetitive pulses even when the inter-pulse interval was reduced. Thus, the number of spikes increased in proportion to the pulse frequency until 9 Hz. When the pulse frequency was further increased beyond 10 Hz, the number of evoked spikes decreased, presumably due to the suppression of evoked response observed for the inter-pulse interval <100 ms.

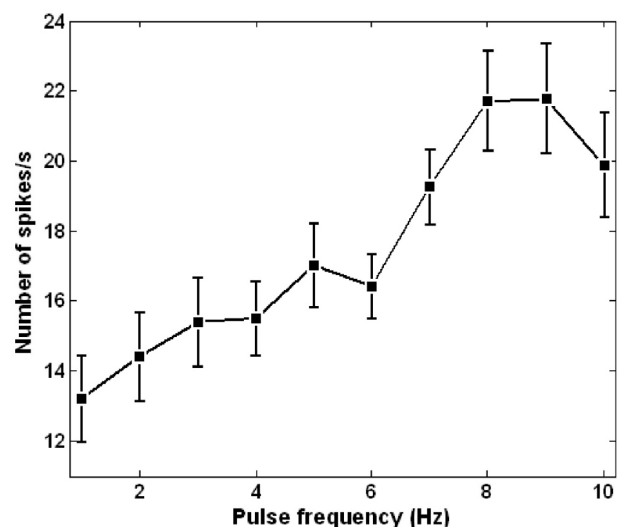


Fig. 6. The RGC response strength as a function of pulse frequency. The results were obtained from 14 RGCs.

## DISCUSSION

The present study investigated the firing characteristics of RGCs in degenerated retina evoked by repetitive stimulation pulses of various inter-pulse intervals. Our purpose was to study the feasibility of pulse frequency modulation as a stimulation strategy for a visual neuroprosthesis, which aims at transmitting visual information. Since the ultimate target of the visual neuroprosthetic devices are patients whose loss of vision is due to retinal degenerative diseases such as RP, we explored the neural responses of RGCs of *rd1* mice, an animal model of RP.

RGC responses to repetitive stimulation pulses have been reported for normal retinas (Fried et al., 2006; Sekirnjak et al., 2006; Jensen and Rizzo, 2007; Ahuja et al., 2008). However, few reports have described RGC responses of degenerated retinas evoked by repetitive pulse stimulations. Due to photoreceptor degeneration, the retinal neural network of *rd1* mice is significantly altered from the normal retina and thus, both spontaneous neural activity and electrically-evoked responses show abnormal characteristics that are significantly different from normal retinas. Presently, distinct rhythmic oscillation was observed in the spontaneous waveforms. The spontaneous firing of RGC spikes was also affected by this oscillation resulting in rhythmic bursting of spikes with the same frequency as the rhythmic field potential (Ryu et al., 2009a). We assumed that the oscillation resulted from the fluctuation of synaptic currents due to abnormally strong excitatory glutamate signaling from bipolar cell to RGC, based on the observation of disappearance of rhythm upon use of a glutamate antagonist (Ye and Goo, 2007). The oscillation remained under electrical stimulation. Electrically-evoked RGC responses also showed rhythmic bursting of spikes with an inter-burst frequency of approximately 10 Hz (Fig. 1B and 1C).

When the dependency of RGC responses on the inter-pulse interval was investigated by applying five successive stimulation pulses, the number of evoked spikes decreased for the later pulses and the degree of the decrease was more pronounced for a shorter inter-pulse interval (Fig. 5). At the inter-pulse interval of 100 ms, 60% of the evoked responses were maintained for the five pulses. These results imply that an inter-pulse interval exceeding 100 ms may be appropriate for a stimulation strategy for visual neuroprosthesis based on pulse frequency modulation. Appropriate range of pulse frequencies could be determined from the tuning curve showing the response strength as a function of pulse frequency (Fig. 6). The response strength showed linearly and monotonically increasing behavior for the frequency range of 1~9 Hz, implying that the intensity of visual information can be represented, or encoded, in RGC responses.

Evoked RGC spikes of *rd1* retina were of two types, i.e., long- and short-latency responses, just as the case of normal retina. The short-latency spikes are assumed to be due to direct stimulation of RGCs. Fried et al. (2006) showed that the short-latency responses of normal retina can follow high frequency stimulation. In this study, we observed that the short-latency spikes could be reliably evoked and can follow high frequency stimulation also in degenerated retina. In addition, we showed that the long-latency spikes can be reliably modulated by pulse frequency, even though their activities are affected by global rhythmic oscillation and shows rhythmic bursting type firing pattern. Apparent suppression of the long-latency responses was revealed

when the inter-pulse interval became <100 ms (Fig. 4). The long-latency spikes were likely evoked by indirect stimulation through synaptic transmission, possibly causing the suppression of responses observed in Fig. 4. In addition, this resulted in the restriction of upper limit for the frequency range for the modulation (Fig. 6). It should be further investigated whether the frequency modulation range determined in this study can provide successful encoding of temporal visual information required for visual perception.

We showed recently that the intensity of visual information can be encoded by population activities of RGCs responding to amplitude-modulated pulse trains (Ryu et al., 2009a; Ryu et al., 2009b). It was found that the strength of long-latency RGC responses can be controlled by pulse amplitude so that the RGC firing rate can be made to follow the temporal pattern of visual input. The result suggests that the pulse amplitude modulation is a feasible means for the stimulation encoding for visual neuroprosthesis. However, the increase of pulse amplitude may result in the increase of the spatial extent of stimulation; i.e., RGCs located far away from the stimulation electrode may also be stimulated as well as those in close proximity. This may cause the deterioration of spatial resolution. The problem would become more serious for multichannel stimulation. Pulse frequency modulation may provide an alternative approach that can solve this problem. Pulse frequency may be modulated to encode the intensity of visual input, while the pulse amplitude is set to activate the RGCs only in close proximity.

Although pulse frequency modulation is a promising strategy for visual neuroprosthesis, some issues should be resolved before clinical trials are undertaken. Power consumption should be much higher compared to the pulse amplitude modulation, since pulse frequency modulation strategy employs much more pulses than the amplitude modulation. High pulse frequency may also cause tissue damage. Accordingly, we should consider a possible tradeoff between these two modulation schemes when designing a stimulation strategy for a visual neuroprosthesis.

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