Contribution of the GABAergic pathway(s) to the correlated activities of chicken retinal ganglion cells

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ARTICLE INFO

Article history:
Accepted 1 July 2007

Keywords:
Multi-unit recording
Population activity
Excitatory
Inhibition

In the present study, the spatiotemporal pattern of chicken retinal ganglion cells' firing activity in response to full-field white light stimulation was investigated. Cross-correlation analysis showed that ganglion cells of sustained subtype fired in precise synchrony with their adjacent neurons of the same subtype (delay lag within 2 ms, narrow correlation). On the other hand, the activities of neighboring ganglion cells of transient subtype were correlated with distributed time lags (10–30 ms, medium correlation). Pharmacological studies demonstrated that the intensity of the medium correlations could be strengthened when exogenous GABA was applied and attenuated when GABA receptors were blocked by picrotoxin. Meanwhile, the GABAergic modulation on the narrow correlations was not consistent. These results suggest that, in the chicken retina, GABAergic pathway(s) are likely involved in the formation of medium correlations between ganglion cells. Neurons might fire at a lower rate but with higher level of synchronization to improve the efficiency of information transmission, with the mechanism involving the GABAergic inhibitory input.

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1. Introduction

The retinal function involves sensing all aspects of visual stimuli, including luminance, color and motion. The information processing first occurs in the retinal circuitry before the signals are further transmitted to the central visual system via optic nerve fibers (Carcieri et al., 2003; Dacey, 1996; Masland, 2001). Retinal ganglion cells are the first stage where visual information is encoded in a form of spiking activities (Dacey, 1996; Meister and Berry, 1999). In this visual pathway, the number of ganglion cells is the fewest among all kinds of neurons, which reflects the necessity that the information processing in the ganglion cells is to re-arrange the information generated from the photoreceptors in a convergent way before the signals are further transferred to the central visual part in a divergent manner. This means that information processed by ganglion cells as independent time-unevolving channels is limited, and compression of visual information is necessary in the ganglion cell layer. There are various ways for the retina to send compressed data to the central visual part, including gain control, adaptation and population activity. Among these, population activity of dynamic groups is an important aspect. Evidence from multi-electrode studies of retina reveals that adjacent retinal ganglion cells of similar functional subtype may fire correlated spikes (DeVries, 1999; Mastronarde, 1983; Meister et al., 1995; Puchalla et al., 2005). The functional contribution of correlated activities has also been reported by a number of authors. Population activity was suggested to represent finer details of spatial information than single neuron’s activity (Schnitzer and Meister, 2003). Other visual stimuli, such as motion, form and texture could also be encoded by the ensemble activity of a group of retinal ganglion cells (see Frechette et al., 2005).

In addition to the function related aspects, the mechanisms underlying the formation of correlated firings are also
widely studied. Various postulates have been proposed. Meister and colleagues noted that there are three types of correlated firings in salamander ganglion cells according to the peak width in the cross-correlation function, with each type dependent on a particular structure of the neural circuitry — the formation of broad (40–100 ms), medium (10–50 ms) and narrow (<5 ms) correlations was attributed to shared signal from photoreceptors, common input from an amacrine cell through gap junctions and electrical coupling between ganglion cells, respectively (Brivanlou et al., 1998; Meister et al., 1995). DeVries (1999) further suggested that the circuitry underlying the correlated activities between ON-ganglion cells and those between OFF-ganglion cells might be different. Morphological studies confirmed the hypothesis forwarded by DeVries that ON-center and OFF-center alpha-ganglion cells show varied tracer coupling patterns (Hu and Bloomfield, 2003; Volgyi et al., 2005).

However, studies about the mechanisms of correlated firings in retinal ganglion cells are mainly focused on the excitatory input that ganglion cells receive from bipolar and

Fig. 1 – Two types of correlated firings. (A and B) The averaged PSTHs of two sustained neurons (bin width 5 ms, 50 repeats). (C) Cross-correlation of firing activities presented in A and B. (D and E) The averaged PSTHs of two transient neurons. (F) Cross-correlation of firing activities presented in D and E. The insertions in C and F illustrate the smoothed curve generated by the BARS method. The dash-dot lines in C and F define the “expected value + 3 SD” bound. The lower traces in A, B, D and E illustrate the time course of the light-ON and light-OFF.

Please cite this article as: Liu, X. et al., Contribution of the GABAergic pathway(s) to the correlated activities of chicken retinal ganglion cells, Brain Res. (2007), doi:10.1016/j.brainres.2007.07.001
amacrine cells (Brivanlou et al., 1998; Mastronarde, 1983; Meis-
ter et al., 1995), the function of inhibitory input from amacrine
cells to the correlation is largely unclear. GABAergic amacrine
cells are important in the retinal network (Brivanlou et al.,
1998; Ishikane et al., 2005). When the activities of ganglion cells
are inhibited by the GABAergic input, two possible changes of
correlation between nearby neurons may occur. One is that the
correlations are weakened while the neuron’s activities are
decreased (Amthor et al., 2005; Meister et al., 1995). The other is
that spikes of ganglion cells become temporally precise in the
presence of suppression, with the refined spikes firing with
higher level of correlations (Chen et al., 2004; DeVries, 1999).

The purpose of the present work is to investigate the
contribution of the inhibitory input mediated by GABAergic
pathway(s) to correlated firings. It was observed that two of
the main types of correlated activities, narrow and medium
correlation, existed between chicken retinal ganglion cells.

Pharmacological studies showed that a majority of the
medium correlations could be strengthened during GABA ap-
plication. On the other hand, when the GABA receptors were
blocked by picrotoxin (PTX), most of the medium correlations
were weakened. This suggests that the inhibitory pathway(s)
may contribute to the formation of this particular type of
correlated firings, while the influence that the GABA inhibi-
tory pathway(s) exert on narrow correlations is not significant.

2. Results

In this study, ganglion cells responded to light-ON or -ON/-OFF
transients of white light flash were investigated. Experiments
were performed on 15 retinas and a total number of 325
ganglion cells were recorded. Correlated firings were detected
from 230 pairs among 559 neuron pairs recorded from adja-
cent (horizontal, vertical and diagonal) electrodes.

2.1. Classification of the chicken retinal ganglion cells

In the retina of newly hatched chicken, most ganglion cells
recorded were activated at both light-ON and -OFF transients.
Only a small number of neurons were pure ON-ganglion cells,
OFF-ganglion cells were rarely recorded. Meanwhile, the dura-
tion properties of these responses were similar to the tran-
sient and sustained subtypes observed in mammalian retinal
ganglion cells (Carcieri et al., 2003). According to the duration
of firing activity in response to sustained stimulus, chicken
retinal ganglion cells can also be classified into transient and
sustained subtypes (see Experimental procedures for details).
Among a total number of 325 ganglion cells recorded, 44.6%
(145 cells) responded to light stimulation with transient ac-

tivities and 55.4% (180 cells) responded with sustained firings.

2.2. Two types of correlated firings among chicken retinal
ganglion cells

Figs. 1A and B show the activities of two adjacent sustained
ganglion cells in response to light stimulation; the cross-cor-
relation function of these two neurons’ firing activities is given in
Fig. 1C. The light responses of two neighboring transient ganglion
cells from another retina are represented in Figs. 1D and E, with

their cross-correlation function being given in Fig. 1F. According
to the τ values estimated (see Experimental procedures), the
correlation type can be classified as narrow (Fig. 1C, τ = 1.41 ms)
and medium (Fig. 1F, τ = 13.07 ms) respectively. In the present
study, narrow correlations were observed from 38.3% (n = 88, 12
retinas) of recorded cell pairs (τ = 1.5 ± 0.5 ms (mean ± SD)), and
medium correlations were observed from 61.7% (n = 142, 12
retinas) of cell pairs (τ = 15.2 ± 5.5 ms (mean ± SD)).

The distribution of correlation time lag in various cell sub-
types was analyzed (Table 1). Narrow type correlations mainly
occurred between sustained ganglion cells (67.1%), while the
medium patterns were predominantly observed from tran-
sient ganglion cell pairs (78.9%).

2.3. Application of GABA enhanced the strength of
medium correlation

In order to investigate the involvement of the GABAergic path-
way(s) in the formation of correlated firings, exogenous GABA
(500 μM) was applied to 3 retinas. Fig. 2 demonstrates the
recordings obtained from two adjacent neurons before, during
and after GABA application. The firing rates of these two cells
were high in normal Ringer’s solution. The peak values in the
PSTH (averaged over 50 trials) of the cells’ responses to light-ON/
OFF transients were 190/130 Hz and 120/150 Hz as given in Figs.
2A and B, respectively. At the mean time, the medium
correlation between these two cells became weak again, with the
peak correlation value being only 0.0225 (Fig. 2I). After GABA
was washed out, each neuron’s responses to light-ON/OFF transients recovered to 170/150 Hz
and after GABA application. The firing rates of these two cells
were high in normal Ringer’s solution. The peak values in the
PSTH (averaged over 50 trials) of the cells’ responses to light-ON/
OFF transients were 190/130 Hz and 120/150 Hz as given in Figs.
2A and B, respectively. But the cross-correlation peak was only
marginally detectable (Fig. 2C). During GABA application, the
firing rates, particularly in response to light-ON transients, were
decreased in both cells (with ON/OFF-response peak values
being 100/150 Hz and 100/150 Hz, respectively), and their
responses were more transient (Figs. 2D and E as compared to
Figs. 2A and B, respectively). At the mean time, the medium

existence of suppression, with the refined spikes firing with
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Table 1 – Distribution of correlation types in various cell
classes

<table>
<thead>
<tr>
<th></th>
<th>S–S</th>
<th>S–T</th>
<th>T–T</th>
</tr>
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<tbody>
<tr>
<td>Narrow (88 pairs)</td>
<td>59 (67.1%)</td>
<td>19 (21.6%)</td>
<td>10 (11.4%)</td>
</tr>
<tr>
<td>Medium (142 pairs)</td>
<td>10 (7.0%)</td>
<td>20 (14.1%)</td>
<td>112 (78.9%)</td>
</tr>
</tbody>
</table>

S–S: correlation between sustained and sustained ganglion cells.
S–T: correlation between sustained and transient ganglion cells.
T–T: correlation between transient and transient ganglion cells.
For those cell pairs that had narrow correlation (19 pairs), the correlations of 15 pairs were increased (169.2%±68.4% as compared to control, p<0.05, paired t-test) and 4 pairs were decreased (63.8%±40.1% as compared to control, p>0.05, paired t-test) during GABA application. The results showed that GABA had no significant influence on them (Table 2).

After-control of GABA application was performed on one retina, in which medium correlations were detected from 15 pairs of neurons. When GABA was added to the retina, the correlation peak value was raised to 187.2%±53.5% as compared to control. Recovery occurred after GABA was washed out, with the correlation peak value returned back to 114.2%±71.3% (compared to control, Fig. 3).

2.4 Application of PTX attenuated the strength of medium correlation

PTX (10 μM) was added to 4 retinas to confirm the influence that GABAergic pathway(s) exerted on the correlated activity between ganglion cells. Fig. 4 gives an example. The two neurons under investigation both showed transient responses in normal Ringer’s solution (with ON-/OFF-response peak values being 100/230 Hz and 120/210 Hz as presented in Figs. 4A and B, respectively); the correlation between the two neurons was of medium type (τ=9.19 ms) with the maximal correlation value being 0.1495 (Fig. 4C). When PTX was applied to the retina, the neurons’ responses to light-ON transients were very much prolonged and lasted for nearly 1 s (with ON-/OFF-response peak values being 140/150 Hz and 140/120 Hz as shown in Figs. 4D and E, respectively); but the peak level of the cross-correlation function (τ=8.16 ms) was clearly reduced, with the maximal value being 0.06277 (Fig. 4F). After PTX was washed out, the light-ON responses of these two cells became transient again (with ON-/OFF-response peak values being 80/150 Hz and 80/200 Hz as shown in Figs. 4G and H, respectively); the maximal value of the medium correlation (τ=6.38 ms) also recovered to 0.1630 (Fig. 4I).

Among all the 37 pairs of cells that had medium correlation (Table 2), the correlations of 34 neuron pairs were attenuated during the application of PTX (54.4%±17.2% as compared to control, p<0.05, paired t-test). In the rest 3 neuron pairs, correlations were strengthened (136.6%±31.2% as compared to control), but these changes were not significant (p>0.05, paired t-test). The application of PTX mainly resulted in a decrease in the medium correlations between transient cells (23 pairs, p<0.05).

At the mean time, the PTX effect on narrow correlations was diversified (Table 2). Correlations were decreased in 15 out of 35 neuron pairs (58.5%±18.8% as compared to control, p<0.05, paired t-test) and increased in the rest 20 pairs (161.3%±49.8% as compared to control, p<0.05, paired t-test).

After-control of PTX application was performed on one retina, in which medium correlations were detected from 15 pairs of neurons. PTX decreases the correlation peak value to 43.0%±19.7% as compared to control. After PTX was washed out, the peak value recovered to 106.2%±41.6% as compared to control (Fig. 5).

Taken together, these results revealed that (1) the firing rate of the neurons became lower during GABA treatment, but the medium correlations were enhanced; (2) when GABA receptors were blocked by PTX, the medium correlations were attenuated although the cells fired more spikes. It seems to suggest that GABAergic pathway(s) may contribute to the formation of medium correlations.

On the other hand, the effect of GABA/PTX treatment was not consistent on narrow correlations.

3. Discussion

3.1 Classification of the retinal ganglion cells

In our experiment, most ganglion cells recorded were activated at both light-ON and OFF transients. Only a very small portion of neurons merely responded to light-ON transient; OFF-ganglion cells were rarely recorded. This might be related to the developmental stage of the retina since the chicken used in our experiments were newly hatched, 3–15 days old.

On the other hand, in parallel to ON vs OFF, ganglion cells can also be classified as transient vs sustained subtypes — which might also be related to functional differences. It has been identified that, in mammalian retina, transient ganglion cells are particularly important for motion detection while sustained ganglion cells are more sensitive to form and fine details (Livingstone and Hubel, 1988; Shapley, 1990), although
it is not yet clear if the chicken retina should exactly follow the same theme.

3.2. Two types of correlated firings mainly occur in different subsets of ganglion cell classes

Correlated firings of neurons play important roles during information processing in visual system. In the present study, two types of correlations, narrow and medium, were observed from chicken retinal ganglion cells. The time lag of the narrow correlations was only 1–2 ms, which suggests that gap junctions other than chemical connections were involved. The distributed time lag (10–30 ms) of medium correlations suggests that it might be related to complicated circuitry mechanisms. Meanwhile, narrow correlations were mostly detected between adjacent sustained ganglion cells while medium correlations were predominantly recorded from neighboring transient ganglion cells (Table 1). Some previous studies revealed that ON- and OFF-ganglion cells are wired with different circuits and could therefore fire with different patterns of synchronized activities (DeVries, 1999; Hu and Bloomfield, 2003; Volgyi et al., 2005). Similarly, different correlation patterns found between sustained and transient ganglion cells in the present study might also involve different neuronal circuitries, particularly the inhibitory pathways (Belgum et al., 1984; Shen and Slaughter, 2001).

3.3. Possible mechanism of medium correlated firings

The fact that in the majority of neuron pairs under investigation the medium correlations can be effectively regulated by exogenous GABA/PTX suggests that the formation of this correlation pattern should involve a mechanism related to the inhibitory pathway(s) mediated by GABA receptors. Generally, nearby ganglion cells can receive two kinds of common input, one is shared excitatory input from bipolar cells and amacrine cells, the other is inhibitory input from amacrine cells. It was previously reported that common excitatory input might be the origin of medium correlations (Brivanlou et al., 1998; DeVries, 1999; Mastronarde, 1983). However, our results seem to imply that the excitatory input might need the fine regulation from GABAergic pathway(s) to generate precise firing activity in the postsynaptic neurons. The inhibitory input reduces the redundant signals when it suppresses the excitatory input. At the mean time, the spike timing is also refined so that the postsynaptic ganglion cells could reach the threshold more quickly when correlated presynaptic inputs are delivered.

Meanwhile, since application of exogenous GABA/PTX can modulate the activities of both GABA A and GABA C receptors, it is still unclear about which particular kind of receptors is involved. Further study applying specific agonists/antagonists is needed.

The effect of GABAergic pathway(s) to narrow correlations is also not clear since neither GABA nor PTX had a consistent influence on this particular kind of correlation (Table 2). The reason might be that the GABAergic inhibitory circuitries which regulate transient and sustained signaling in ganglion cells are different (Shen and Slaughter, 2001).

3.4. Possible physiological significance

Neurons “talk” to each other via synapses. Presynaptic input can result in graded membrane potential changes in postsynaptic neuron. If the postsynaptic neuron receives a sequence of input from its presynaptic neurons, temporal summation of the postsynaptic membrane potential changes should occur before the postsynaptic neuron fires an action potential. However, if the presynaptic neurons fire in synchrony, the signal transmission should be more efficient because of the spatial summation, in a sense that the threshold for postsynaptic action potential will be lower and the time delay between presynaptic and postsynaptic action potentials will be shorter (Azouz and Gray, 2000). Synaptic information transmission might be more effective and energy saving when the correlated spikes exist (Konig et al., 1996; Pouille and Scanziani, 2001).

In the present study, our results also suggest an economy of energy which is related to correlated activities. In the chicken retina, the activation of GABAergic pathway(s) allows the ganglion cells to fire more correlated spikes, rather than just reduce their firing rate, which provides higher transmission efficiency. Under such situation, the visual information transmission could be more efficient and reliable.
4. Experimental procedures

4.1. Electrophysiology recording

Fifteen retinas from newly hatched chicks (3–15 days post hatching) were investigated in this study. Experimental operations followed that were described in our previous reports (Chen et al., 2004; Zhou et al., 2005). All procedures strictly conformed to the humane treatment and use of animals as prescribed by the Association for Research in Vision and Ophthalmology. After decapitation and enucleation of the eye, the eyeball was hemisectioned with a fine razor blade, the vitreous body and cornea were removed carefully. To record the spike trains of retinal ganglion cells, a small piece (4×4 mm²) of isolated retina was placed on a multi-electrode array (MEA60, MCS GmbH, Germany) with the ganglion cell side contacting the electrodes. The MEA consisted of 60 electrodes (10 μm in diameter) arranged in an 8×8 matrix (leaving the 4 corners void) with 100 μm tip-to-tip distances (horizontal and vertical). For a better contact between the array and the retina, a small quantity (3 μl) of nitrate cellulose solution (1.0 mg Sartorius cellulose nitrate dissolved in 10.0 ml methanol) was smeared onto the electrode array as electrode glue and the retina was placed on the array after methanol was vaporized. The preparation was perfused in oxygenated (95% O2 and 5% CO₂) Ringer’s solution (containing in mM: 120.0 NaCl, 5.0 KCl, 3.0 MgCl₂, 1.8 CaCl₂, 25.0 NaHCO₃, 1.2 HEPES, 25.0 glucose) with a pH value of 7.5±0.2. The tissue and perfusate were kept at 38 °C by a temperature control unit (Thermostat HC-X, MCS GmbH, Germany). A small Ag/AgCl pellet with wire was immersed into the bath solution and acted as the reference electrode. In the pharmacological studies, 500 μM GABA (Sigma, USA) and 10 μM picrotoxin (Sigma, USA) were applied. The neuronal photoresponses were recorded simultaneously by the multi-electrode array, and the signals were amplified through a 60-channel amplifier (single-ended amplifier, amplification 1200×, amplifier input impedance >10¹⁵ Ω, output impedance 330 Ω). Signals from the selected channels along with the stimulus were sampled at a rate of 20 kHz (MCRack) and stored in a Pentium IV based computer. Spikes from individual neurons were sorted based on principal component analysis (PCA) (Wang et al., 2006; Zhang et al., 2004) as well as the spike-sorting units in the commercial software MCRack (MCS GmbH, Germany) and OfflineSorter (Plexon Inc. Texas, USA). In order to get accurate data for cross-correlation analysis, only single-neuron events clarified by all these methods were used for further analyses in the present study.

4.2. Stimulus

Spatially uniform white light was generated from a video monitor (796 FD II, MAG) and was focused to form a 0.75 x 0.75 mm² image on the 60-channel amplifier via a lens system at a certain photonic mean intensity (II1400, USA). Full-field sustained white light (6.09 nW/cm²) was given for 30 s before the stimulation protocol was applied, the purpose of which is to adjust the sensitivity of the ganglion cells to a similar level. Stimulus consisting of full-field white light (12.18 nW/cm²) duration of 1 s and dark interval of 9 s was given repeatedly for 50 times after the adaptation was completed (Zhou et al., 2005).

4.3. Classification of chicken retinal ganglion cells

The ganglion cells can be classified into different subtypes according to their physiological characteristics. In our experiment, most ganglion cells recorded were activated at both light-ON and -OFF transients. However, the neurons can be divided into two groups according to the duration of firing activity in response to sustained light illumination, following a method similar to that employed by Carcieri et al. (2003).

While doing data analysis, the ON part of the PSTH is firstly smoothed by a non-parametric regression method Bayesian Adaptive Regression Splines (BARS) (Kass et al., 2003; Ventura et al., 2002). The peak value of the curve is defined as its amplitude A. The response duration T is defined as the time over which the response decays from A to A/e (Fig. 6). Then, the response duration T was used as the first parameter to divide the ganglion cells into two main classes. Those neurons with T values shorter than 10 ms or longer than 30 ms were classified as “transient” and “sustained” cells, respectively. This is somewhat arbitrary, but a majority of neurons can be clearly classified. For the rest neurons (35%) whose T values were between 10 ms and 30 ms, further analysis was performed — if the cell’s firing rate does not decay to zero after 4T, the cell is classified as “sustained”, otherwise a “transient” cell is identified.

4.4. Cross-correlation analysis

The synchronized firings between pairs of chicken retinal ganglion cells were analyzed using cross-correlation function, which reflected the mean firing activity of one cell as a result of the activity of another.

Generally, the cross-correlation function is defined as:

\[ c_{xy}(m) = \sum_{n=0}^{N-|m|-1} x_n y_{n+m} R_{-m} \]

for \( m \geq 0 \) and \( R = \sum_{l=1}^{N} x_l^2 \sum_{l=1}^{N} y_l^2 \)
where $x_n$ denotes the value of sequence $x$ at moment $n$; $y_{n+m}$ is the value of sequence $y$ at moment $n+m$; $c_{xy}(m)$, by definition, represents the correlation between sequences $x$ and $y$ with a lag of $m$, which reflects the effect signal $x$ exerts on signal $y$ with a time delay $m$; $R$ is the normalizing factor.

When two neurons are stimulated simultaneously, the firing rates of both cells are elevated. Such increased activities may result in increased synchronized firings between them. So the correlation between the two spike sequences may include two components, with one corresponding to real correlated activities due to the functional wiring, and another due to the co-variation in firing rates of the two cells examined. The latter part can be corrected via a shift predictor, which is computed similarly to the cross-correlation function, except that one trial of a certain spike train corresponds with a shifted trial of the other spike train (Pauluis et al., 2001; Perkel et al., 1967). The peak of the corrected cross-correlation function is considered significant if the peak value exceeds expected value by 3 standard deviations (Pauluis et al., 2001).

In order to specify the characteristics of the correlations, the peak width ($\tau$) of the cross-correlation function was estimated. Since the cross-correlation functions were quite “noisy”, statistical analysis with “null hypothesis” being “zero-mean normal distribution” was performed to identify those values that were not significantly different from “zero” and have them eliminated before further estimation was performed (see Figs. 7A and B). The range of the identified “non-zero” parts is indicated in Fig. 7A (between two arrows), with its width being $W$ (Fig. 7B). Then the region around the peak ($\pm 2W$ around zero) was chosen for further analysis. Those negative values in the remaining data set were also eliminated (see Fig. 7C). BARS method was then applied to generate a smooth curve to describe the distribution of time lags of the cross-correlation function (Kass et al., 2003; Ventura et al., 2002). The maximal value of the curve is defined as its amplitude $P$, $T_1$ and $T_2$ are those time lags by which the correlation strength decays to a value of $P/e$, time lag distribution coefficient (peak width) $\tau$ is defined as the difference between $T_2$ and $T_1$ (see Fig. 7C).

$P$, $T_1$ and $T_2$ are those time lags by which the correlation strength decays to a value of $P/e$, time lag distribution coefficient (peak width) $\tau$ is defined as the difference between $T_2$ and $T_1$.

**Fig. 6** – Classification of chicken retinal ganglion cells. Gray bars show the ON part of the averaged PSTH of one ganglion cell’s light response (bin width 5 ms, 50 repeats). Solid line shows the smoothed curve generated by the BARS method. A: the maximal value of the curve; $T$: the duration of light response.

**Fig. 7** – Estimation of the distribution coefficient ($\tau$) of correlation time lags. (A) The original cross-correlation function. (B) Truncated data set as indicated by the box in A. $W$: the width of the “non-zero” parts. (C) The non-negative part of B (with the negative values discarded) is fitted using BARS method. $P$: the maximal value of the curve; $T_1$ and $T_2$: those time lags at which the cross-correlation values reach $P/e$; $\tau$: the time lag distribution coefficient.
Acknowledgments

This work was supported by grants from the State Key Basic Research and Development Plan (No. 2005CB724301), National Foundation of Natural Science of China (No. 30670519) and the Ministry of Education (No. 20040248062).

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Please cite this article as: Liu, X. et al., Contribution of the GABAergic pathway(s) to the correlated activities of chicken retinal ganglion cells, Brain Res. (2007), doi:10.1016/j.brainres.2007.07.001