Intracellular and current source density analysis of pretectal input to the optic tectum of the frog

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Abstract: Objective Electrophysiological examination of the ipsilateral pretectotectal projection has proved that pretectal cells elicit strong suppressive responses to the ipsilateral tectum. However, the neural mechanisms underlying the contralateral pretectotectal projection are still obscure. The present study aimed to examine the synaptic nature of pretectal nuclei and contralateral tectal cells, and to demonstrate the spatiotemporal pattern of neuronal activity in the 2 main brain structures. **Methods** Intracellular recording and current source density (CSD) analysis were used to test the complexity of neuronal mechanism of pretectotectal information transfer. **Results** The pretectal stimulation elicited only one type of response on the contralateral tectum, the inhibitory postsynaptic potential (IPSP). The majority of contra-induced IPSPs were assumed to be polysynaptically driven. In the CSD analysis, only one sink with short latency was observed in each profile. The ipsilateral projection produced a prominent monosynaptic sink in layer 8 of tectum. Recipient neurons were located in layers 6 and 7 of tectum. The result confirmed former findings from ipsilateral intracellular recordings. **Conclusion** These results suggest the following neuronal circuit: afferents from the pretectal nuclei broadly inhibit both tectal neuron, and since no second sink occurs in tectal layers, the pretectotectal excitatory afferents probably do not extend over the whole tectum, but are within limited state. The results of intracellular recording and CSD analysis further provide evidence of how pretectal afferent activity flows within the tectal laminae.

Keywords: intracellular recording; current source density analysis; optic tectum; frog

1 Introduction

The optic tectum of frog is known to be an important visual and auditory center. Being analogous to mammalian superior colliculus, it has been a subject of electrophysiological, morphological and behavioral studies^[1-10]. The optic tectum is composed of 9 layers numbered from 9 (superficial

layer) to 1 (periventricular layer)^[11,12]. The laminar organization comprises alternate fibrous (layers 1, 3, 5, 7 and 9) and granular (layers 2, 4, 6 and 8) layers. Most of the tectal neurons are located in layers 8 and 6. The thickness of the optic tectum is approximately 800 μm . The depths of layers 9, 8, 7 and 6 are approximately 0-350 μm , 350-450 μm , 450-500 μm , and 500-600 μm , respectively, while layers 5-1 are 600-800 μm in depth. In the superficial layers 9-7, the terminals of pretectal cells make synapses with the dendrites of tectal cells, whose cell bodies are located in deeper layers such as layers 8 and 6.

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Morphological and neuroanatomical studies have revealed that the pretectal nuclei of the frog receive input from the ipsi- and contralateral tecta and project back to both optic tecta^[11,13-15]. Behavioral experiments demonstrate that ablation of the pretectal thalamus leads to hyperactive prey-catching in response to any moving visual stimulus including very large objects that are normally avoided^[3,16,17].

As revealed by a former report on the ipsilateral pretectotectal projection by Kang *et al.*^[18], stimulation of the pretectal nuclei elicits mainly inhibitory responses on ipsilateral tectal cells. Those ipsi-induced inhibitory postsynaptic potentials (IPSPs) are found to be monosynaptic and disynaptic/polysynaptic driven events^[17]. However, there are very few physiological studies on the contralateral pretectotectal projection. In the present study, the synaptic nature of contralateral pretectotectal information transformation was investigated by intracellular recording.

In order to clarify the synaptic connection patterns of ipsi- and contralateral pretectotectal projections at the mass response level, current source density (CSD) analysis was used to investigate the field potentials (FPs) evoked by electrical stimulation of pretectal nuclei. The CSD method has been applied in the studies of the central nervous system of mammals, especially the cat visual cortex^[18-25]. In vertebrates, CSD analysis can also reveal many essential properties of neuronal circuits^[26-31]. Thus, when studying neuronal mass actions via FPs, submitting the original data to CSD analysis is proved to be very helpful, since this method not only reveals the sites of excitatory synaptic interactions and locations of cell somata, but also discloses even subthreshold synaptic events. Moreover, it assesses the major, basic pattern of activity rather than individual cell responses.

2 Materials and methods

2.1 Animals Adult bullfrogs, *Rana catesbeiana* (of either sex, weighting 100-300 g) were kept in laboratory tanks under a 12:12 h light/dark cycle. They were fed on chicken liver twice a week.

2.2 Preparations Animals were anesthetized by injection of tricaine methanesulfonate (MS222, Sigma; 0.02 mg/g body weight), and paralyzed by injection of succinylcholine

(Succin, Yamanouchi; 0.02 mg/g body weight). Then the animal was placed on a metal frame, and its body was covered with gauze to facilitate cutaneous respiration. After local infiltration of anesthetic (Xylocaine, Fujisawa) into the skin of the head, the skull was opened, and optic tectum and diencephalons were surgically exposed by careful removal of bone with a dental drill and retraction of the dura mater and the arachnoidea with fine forceps and scissors. All the experiments were carried out at room temperature (18-22 °C).

2.3 Electrical stimulation Tungsten bipolar stimulus electrodes were inserted stereotaxically into the left pretectal lateral posterodorsal (Lpd) and posterior (P) thalamic nucleus (Lpd/P region). The electrode tips were uninsulated for 0.1 mm, and separated by 0.15-0.2 mm. For Lpd/P stimulation, rectangular pulses of 100 μ s duration were delivered. After the intracellular recordings, DC current (20 μ A) was passed for 20-30 s through the stimulating electrode to verify its position. Verification of the electrode position was performed as previously reported^[18].

2.4 Recording FPs in response to pretectal stimulation were recorded with micropipettes filled with 2 mol/L NaCl. Before recording, the pipette tips were broken under a microscope. After breaking, the diameter of the tips was approximately 10 μ m, and the resistance ranged from 500 k Ω to 1 M Ω . The recording electrode was connected to a high input impedance preamplifier (MEZ-7200, Nihon Koden) followed by a biophysical amplifier (DPA-200, Dia Medical System). FPs in response to electrical stimulation of pretectal nucleus were recorded from the ipsilateral and contralateral optic tectum. Potentials were measured from the tectal surface to a depth of 800 μ m, with 20- μ m steps. At each recording site, 10 consecutive recordings were stored at a data recorder (PC-108M, Sony) for later analysis.

2.5 Data processing and CSD analysis All recorded potentials were digitized (ADM-682PCI, Micro Science) at 10 kHz for later analysis. After the experiments, data were processed with an IBM compatible computer. For the postsynaptic potentials and surface potentials, the latencies after stimulation were measured.

The computational algorithm of CSD analysis^[24,20,32] was applied to the sets of FPs recorded from whole tectal layers

at 25 μm or 50 μm steps. The CSD depth profile was calculated as below.

Based on the validity of Ohm's law in the extracellular space and on the assumption that the electrical field is quasi-static, the current density of source and sink in the brain consisting of cortical layers was expressed as the following: $I_m = \nabla_\sigma \nabla_\phi$, where I_m is the current source density, σ is conductivity and ϕ is the FPs^[33]. In the optic tectum, it is assumed that the FPs are invariant in the 2 horizontal dimensions parallel to the tectal layers^[29] and that the tissue conductivity tensor is isotropic and homogeneous^[22,34]. These assumptions lead to the following simple formula: $I_m = \sigma_z \frac{\partial^2 \theta}{\partial z^2}$, where z is the depth axis perpendicular to the cortical layers. The intratectal resistance can be considered to be almost constant^[32,35]. Thus, the relative CSD (I'_m) profiles could be calculated by the following formula: $I'_m = \frac{\partial^2 \theta}{\partial z^2} \approx \frac{\theta(z + n\Delta_z) - z\theta(z) + \theta(z - n\Delta_z)}{(n - \Delta_z)^2}$, where θ is the extracellular FPs, z is the coordinate perpendicular to the layers, Δ_z is the sampling interval (25 or 50 μm in the present study) and $n\Delta_z$ is the differentiation grid (n is usually set to 3 or 4).

2.6 General aspects Initially, FPs were recorded from both optic tecta in response to pretectal stimulation. In order to show the horizontal distribution of pretectal input to the optic tectum, surface potentials were recorded. To show the vertical distribution, CSD analysis was applied to FPs recorded by vertical penetration. Next, to demonstrate the synaptic nature of pretectal input to the contralateral tectum, postsynaptic potentials were recorded intracellularly from the contralateral tectal neurons. Intracellular recordings and FPs were analyzed in the present study.

3 Results

3.1 Surface potentials In 5 frogs, FPs evoked by electrical stimulation of pretectal nuclei (Lpd/P) were recorded from the surface ($< 300 \mu\text{m}$) of both tecta at all the 9 positions (A-I). The spatial distribution of pretectally evoked FPs across the 9 tectal recording sites was shown in Fig. 1 and Fig. 2. Under a certain current, the FPs from these loci were similar in size, amplitude, and sequence of the wave components.

In most recording sites, the FPs showed a negative N wave containing 2 superimposed subcomponents (Fig. 1, arrow). Above a certain current, the amplitudes and the components of FPs remained unchanged, probably due to the quantitative activation of the respective structures in the stimulus area (Lpd/P region).

Regarding the amplitude of the negative N wave, the following hierarchy was obtained for the recording sites: $F = E > H = I = B > G > C > D > A$ for the ipsilateral tectum, and $F > E > I > C > B > H > A > D > G$ for the contralateral tectum. Both the amplitude and shape of FPs were largely different between the ipsilateral and contralateral tecta. The region of best activation thus corresponded to a portion of the dorsomedial visual field.

3.2 Polarity of electrical activity The laminated structure of the optic tectum contains the dendritic trees mainly in the superficial layer and the corresponding somata in deeper layers. Therefore, synaptic input will lead to different electric dipoles arranged perpendicularly to the tectal surface. On stimulation of the pretectal nuclei (Lpd/P), only one type of profile was recorded in the ipsilateral tectum. The dominant component of the evoked potential is the surface-negative deflection (the N-wave). In deeper regions of the tectum, this negative potential first increased in amplitude and then decreased, reversing polarity to a positive potential at the depth of approximately 380-400 μm (Fig. 3A). In some penetration, no reversal could be observed. Probably, current dipoles were too small to produce detectable reversal of amplitudes. No reversal current dipoles were observed in the contralateral tectum.

However, it is difficult to determine from FPs alone the laminar location of this activity and to what extent it depends on direct or indirect pretectal inputs. As described below, such information was readily extracted from the CSD records.

3.3 CSD analysis Ten depth profiles of FPs were recorded from the surface to 800 μm in depth, ipsilateral to the stimulated pretectal nucleus. Five profiles were subject to CSD analysis. A typical result was shown in Fig. 3B. These CSD profiles showed the same basic spatiotemporal distribution with only one current sink in the tectum. The sink was labeled "a" in Fig. 3B, occurring over a distance of about

Fig. 1 Distribution of tectal surface FPs recorded from the standard grid (A-I) in response to electrical stimulation in the ipsilateral pretectal Lpd/P region. Each trace represented 3 subsequent superimposed records. S, stimulation electrode. OT, optic tectum. TH, thalamus.

340-360 μm in the middle part of tectal laminae. The onset latency of this sink was 2.0 ms. In all CSD depth profiles, clear sinks and sources were recognized at similar depths. The sink appeared at the depth between 320-480 μm with a latency of 2.0-2.8 ms, and the source appeared in the depth between 380-520 μm . No significant sink and source were found in any of the depth profiles in the contralateral tectum.

3.4 Postsynaptic potentials A total of 31 tectal neurons were intracellularly recorded in response to contralateral Lpd/P nuclei stimulation. The membrane potentials of the impaled neurons ranged from -30 mV to -60 mV. Usually, the neurons located superficially with small somata had lower resting potentials than the deeper large neurons did. Recordings with considerable changes in resting potential or with durations less than 1 min were eliminated from the present sample.

In the contralateral tectum, the pretectal Lpd/P stimulation evoked only a pure IPSP followed by neither a hyperpolarizing wave nor a depolarizing wave, even under higher stimulus intensities (Fig. 4A). The durations and amplitudes of these IPSPs were similar to those described for ipsilateral recordings^[18]. There was no obvious difference in response properties between the ipsilaterally and contralaterally evoked IPSPs.

3.5 Latency and depth distribution As shown in Fig. 4B, latencies of IPSPs induced by contralateral pretectal stimulation ranged from 4.2 ms to 14.1 ms, with an average latency of (10.1 ± 3.10) ms ($n=31$). Apparently, there were 2 separate groups. In the shorter group, the latencies ranged from 4.2 ms to 7.2 ms, while in the longer group, the latencies ranged from 9.3 ms to 14.1 ms. The minimal latency of the IPSP evoked

Fig. 2 Distribution of tectal surface FPs from the standard grid evoked by contralateral pretectal Lpd/P stimulation. S, stimulation electrode. OT, optic tectum. TH, thalamus.

by the contralateral stimulation was longer than that by the ipsilateral stimulation (1.5 ms)^[18].

IPSP latencies were plotted against depth in Fig. 5B. No obvious relationship was found between latency and depth. The majority of cells were located between 200 μ m and 700 μ m. The depth distribution indicated that pretectotectal fibers connect with tectal neurons in a wide range of layers (including layers 9-6). Although the tectal cell layers are laminated (Fig. 5A), this was not reflected in the scattered recording sites as shown in Fig. 5B, which might result from the errors in reading the depth by the micromanipulator.

4 Discussion

Although the anatomy and physiology of pretectotectal pathways especially the contralateral projection have been reported, synaptic connection patterns between tectal neurons and pretectotectal fibers have remained unknown. The present study demonstrates the synaptic organization intracellularly between the pretectal thalamus and the optic tectum in frogs. It provides useful cues to formulate the neuronal circuitry in the 2 important brain structures related to visual and auditory information processing.

Previous immunocytochemical studies by Kozicz and

Fig. 3 A: FPs evoked by electrical stimulation of the ipsilateral pretectal nuclei (Lpd/P). These were obtained in successive depth in steps of 20- μ m intervals in a vertical track through the optic tectum. Each sweep is an average of 10 responses. B: The CSDs extracted from the same averaged field potentials in A. For each individual trace, upward deflection indicated sink (filled with black color), and downward deflection indicated source (filled with gray color). The sinks represented excitatory synaptic activities. Current sink (labeled "a") is mainly located in the middle of the tectal layers. Arrows at the top of records indicate time of stimulation. FP: field potential. CSD: current source density.

Lázár have revealed that the pretectal Lpd/P nuclei contain neuropeptide Y (NPY)-like immunoreactivity cells whose fibers are distributed in the superficial layers of ipsilateral tectum^[36]. It is known that NPY can reduce the excitatory input. However, they did not conduct the immunocytochemical studies of contralateral pretectotectal projections. An earlier study by Matsumoto^[9] demonstrated the pretectal cells in Lpd/P, whose bifurcating axons project bilaterally to tectal layer 9. It is likely that the pretectal fiber projecting to contralateral tectum is related to NPY.

Stimulation on pretectal Lpd/P nuclei exerts only IPSPs in the contralateral tectum. The inhibitory responses (IPSPs) can be used to explain the disinhibition in the optic tectum caused by mechanical, electrolytical, or axon sparing chemical lesions applied to the pretectal Lpd/P region^[3,37]. Lesions to the pretectal Lpd/P region in toads lead to hyperactive prey-catching in response to any moving visual stimulus

including very large objects that are normally avoided^[37]. In our study, the impaired tectal cells exhibit inhibitory responses to contralateral pretectal (Lpd/P) stimulation. Combined with the ipsilateral intracellular recordings^[18], we conclude that the pretectal nucleus exert a strong suppressive influence on both tecta, which is consistent with a previous behavioral study^[3].

As shown in Fig. 4B, the minimal latency of the IPSP evoked by the contralateral stimulation was longer than the minimal latency of the ipsi-induced IPSP^[18]. This probably originates from the difference of projecting distance of pretectal cells to ipsi- and contralateral tecta. The longer group (9.3-14.1 ms) is assumed to be a polysynaptically driven event. It would be important to know whether the inputs to ipsilateral and contralateral tecta from the pretectal nuclei converge onto the same tectal cells, but our experiment was not designed to answer this question.

Fig. 4 A: Intracellular recordings of responses elicited by contralateral pretectal (Lpd/P) stimulation. Superimposed traces were from 5 different tectal cells. Lower traces under postsynaptic potential indicate field potentials recorded immediately after loss of the cell. The arrow indicates the onset of the electrical stimulation. B: Latency histograms of postsynaptic potentials in tectal cells in response to electrical stimulation of contralateral Lpd/P region.

Although the anatomy and physiology of pretectotectal pathways, especially the ipsilateral projection, have been widely studied, synaptic spatiotemporal connection patterns between tectal neurons and pretectotectal fibers still remain unknown. The main reason is that the physiological recording is restricted to either fiber terminals or cell bodies. CSD analysis enables us to elucidate the vertical extension of the neurons from cell body to distal dendrite as well as layers of synaptic contacts. Thus, the present experiment is complementary to single unit and intracellular studies.

Many experimental and theoretical studies strongly suggest that sinks and sources shown in CSD depth profiles mainly reflect excitatory postsynaptic currents (EPSCs)^[20,24]. In a former study of ipsilateral intracellular recordings^[18], the rising phase of IPSPs was at least 5 times slower than that of EPSPs. This means that IPSCs, being proportional to dV/dt of the IPSPs, are very small compared to EPSCs. Thus, our present results in the frog optic tectum support the hypothesis that inhibitory synaptic connections scarcely contrib-

Fig. 5 A: Drawing of the tectal laminar organization. The depth and corresponding layer number are shown. The letters R1, R2, R3 and R4 indicate the projection layer of retinal afferent of each class. B: Depth-latency relationship for contralateral recordings.

ute to the CSD.

Ipsilateral pretectotectal afferents are distributed in laminae B, D, F of layer 9 and in layer 8 as cited earlier^[36]. In ipsilateral optic tectum, typical sink and sources were found (Fig. 3B), appearing from 320 μm to 480 μm (layers 9-6) and from 380 μm to 520 μm (layers 8-6), respectively. These findings indicate that the recipient neurons extended from 320 μm (distal dendrite) to 580 μm (cell body), covering layers 9-6. In these neurons, the terminal sites indicated by the sink are layers 9-6. In the superficial layer (layer 9), only very weak sinks are sparsely distributed. This result implies that the majority of the ipsilateral pretectotectal fibers found abundantly in layer 9 are inhibitory. This is consistent with the immunocytochemical studies showing that NPY-immunoreactive cells in pretectal optic tectum project to the ipsilateral

Fig. 6 A schematic diagram of the intratectal excitatory relay. Together with the intracellular recording results, the excitatory activity caused by pretectal afferent is inhibited rapidly, and kept in limited state. Here, blank circles indicate the excitatory synapse, and black circles indicate the inhibitory synapse.

optic tectum where they connect to non-efferent interneurons^[36]. For better comparison of pretectotectal projections, the results of this study and those from a previous study^[18] are schematically illustrated in Fig. 6.

Matsumoto *et al.*^[13] have reported that large ganglionic neurons of bullfrog in layer 6/7 vigorously fire in response to visual stimulation and that their axons extend to the medulla oblongata. These findings indicate that the large ganglionic neurons are output neurons to the descending motor pathway for both prey catching and avoidance behavior. One important finding in this study is that large ganglionic neurons in layer 6/7, but not the other neurons, receive strong excitation from both retinotectal and pretectal afferents^[13]. The existence of such a neuronal circuit indicates that pretectal nuclei produce positive feedback to the output neurons of the ipsilateral optic tectum. The finding also suggests the existence of a positive feedback circuit within the optic tectum. Thus, feedback to the output neurons strengthens the visually elicited responses. The influence of pretectal

nucleus on the contralateral large ganglionic neurons remains unknown and requires further study.

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青蛙前视盖与视顶盖间神经传导的细胞内记录和电流源密度分析

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摘要: **目的** 电生理研究已经证实青蛙前视盖对同侧视顶盖细胞有强烈的抑制作用, 但其与对侧视顶盖间神经活动的特性目前尚不清楚。本研究旨在探讨青蛙前视盖与视顶盖之间复杂的神经活动机理, 并对这种神经活动的时空方式进行分析。**方法** 用细胞内记录方法, 通过电刺激前视盖的神经细胞核来记录对侧视顶盖细胞的神经活动。通过电流源密度分析方法解析细胞外记录的视顶盖细胞的神经活动。**结果** 前视盖的电刺激只引起了对侧视顶盖的一种应答, 即抑制性突触后电位(inhibitory postsynaptic potential, IPSP), 且大多数的 IPSPs 是通过多突触方式进行神经信息传递的。此外, 电流源密度分析结果显示, 前视盖刺激在同侧视顶盖上唤起了非常微弱的兴奋性神经活动, 这与以前的细胞内研究结果相一致。**结论** 前视盖的神经细胞能强烈抑制双侧视顶盖细胞的神经活动。细胞内记录和电流源密度分析结果有助于进一步揭示前视盖传入在视顶盖层的传导情况。

关键词: 细胞内记录; 电流源密度分析; 视顶盖; 青蛙