



## MANIPULATION OF INHIBITION IN THE OWL'S NUCLEUS LAMINARIS AND ITS EFFECTS ON OPTIC TECTUM NEURONS

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**Abstract**—Differences in arrival time and intensity (or level) of sound between the ears serve as cues for localization of sound in many animals. Barn owls use interaural time difference (ITD) and interaural level difference (ILD) for localization in azimuth and elevation, respectively. The owl's brain processes these two cues in separate pathways. The nucleus laminaris is the first site that detects ITDs by methods of delay lines and coincidence detection. The nucleus ventralis lemnisci lateralis, pars posterior is the first site of processing ILDs. The two pathways merge in the inferior colliculus to give rise to sensitivity to combinations of ITD and ILD. This selectivity is relayed to the optic tectum where neurons are sensitive to both visual and auditory stimuli. The present paper reports the results of manipulating inhibition in the nucleus laminaris and its effects on the optic tectum neurons. Injection of GABA or muscimol (a GABA<sub>A</sub> receptor agonist) in the nucleus laminaris reduces the responses of its neurons to ITD. This finding proves that GABA<sub>A</sub> receptor-mediated inhibition acts on the nucleus laminaris neurons. The same treatment did not affect the neurons of the nucleus ventralis lemnisci lateralis, pars posterior, whereas it reduced the response of the optic tectum neurons to ITD–ILD pairs.

We conclude that although the two pathways are independent, the process of combining ITD and ILD creates a new relationship in which the output of the neuron varies with the amplitude of either input. This conclusion is consistent with the recent finding that the combination sensitivity is due to a multiplication of ITD and ILD inputs. © 2002 IBRO. Published by Elsevier Science Ltd. All rights reserved.

*Key words:* barn owl, GABA, inhibition, nucleus laminaris, optic tectum.

Barn owls use differences in arrival time and amplitude (or level) of sound signals between the ears to localize their sources. The time disparity is referred to as the interaural time difference (ITD) and the amplitude disparity as the interaural level difference (ILD). Owls use ITD for localization in the horizontal direction and ILD for the vertical direction. The owl's auditory system processes ITD and ILD in separate pathways that start in the cochlear nucleus magnocellularis (NM) for time and the cochlear nucleus angularis (NA) for amplitude. The first site of ITD processing is the nucleus laminaris (NL), which receives input from the left and right NM. The first site of ILD processing is the nucleus ventralis lemnisci lateralis, pars posterior (VLVp), which receives excitatory input from the contralateral NA and inhibitory input from the ipsilateral NA by way of the contralateral VLVp. These two pathways merge initially in the lateral shell of the central nucleus of the inferior colliculus (LS),

completing the merger in the external nucleus of the inferior colliculus (ICx). This convergence gives rise to selectivity for combinations of ITD and ILD in ICx and its target areas including the optic tectum (OT) (Knudsen, 1984). The present paper concerns inhibition in NL as well as the effects of manipulating it on the response of OT neurons to combinations of ITD and ILD. Fujita and Konishi (1991) referred to an unpublished observation in which injection of bicuculline into the NL of an owl greatly reduced the response of neurons to ITD in the core of the central nucleus of the inferior colliculus. If this finding can be replicated, it provides the first *in vivo* evidence for GABAergic inhibition in NL.

This study also addresses another early finding in which a reduction of response in the cochlear nucleus changed the selectivity of ICx neurons for either ITD or ILD but not both depending on which nucleus, NM or NA, was affected (Takahashi et al., 1984). This work led to the idea that ITD and ILD were processed independently. However, the independence applies only to ITD or ILD selectivity but not to the amplitude of responses. The strength of response of ICx neurons to ILD declined as a result of reducing activity in NM. Does this indicate that the processing of one cue is not completely independent of that of the other cue? We analyze this important issue further in this paper, because it was not taken up in the work cited above. We will first examine whether a reduced activity in any part of the time pathway, NL in this case, lowers the

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*Abbreviations:* EPSP, excitatory postsynaptic potential; ICx, external nucleus of the inferior colliculus; ILD, interaural level difference; ITD, interaural time difference; LS, lateral shell of the central nucleus of the inferior colliculus; NA, nucleus angularis; NL, nucleus laminaris; NM, nucleus magnocellularis; OT, optic tectum; VLVp, nucleus ventralis lemnisci lateralis, pars posterior.

amplitude of responses to ILD in neurons of the OT that receives direct input from ICx. We will then show that the lowered amplitude is not due to a direct effect of the drug injected into NL. A recent intracellular study of ICx neurons shows that their sensitivity to combinations of ITD and ILD is due to a multiplication of synaptic inputs from the two pathways (Peña and Konishi, 2001). This fact explains why a reduced input from the time pathway causes a reduced response to ILD in ICx neurons. The multiplicative process was shown by mathematical analyses of subthreshold postsynaptic potentials. The present paper provides evidence for an interaction between the ITD and ILD inputs, although it does not discriminate between multiplication and addition. This evidence is new, because it comes with appropriate control experiments and because it is based on direct manipulation of one input.

## EXPERIMENTAL PROCEDURES

### *Surgery and animal care*

Owls were anesthetized with Ketamine (10–20 mg/kg) for all surgical operations. All surgical tools were sterilized. This project required the cementing of a small inverted T-shaped stainless steel plate on the skull. This plate was used for holding the head at a desired angle (70°) during recording experiments. In addition to the general anesthetic, a local anesthetic (1% lidocaine hydrochloride; Xylocaine) was injected subcutaneously before an incision was made on the scalp. The owl's skull consists of two layers separated by bony trabeculae. For the placement of the head plate, only a small area of the first layer was removed and the hole was filled with dental cement onto which the plate was gently lowered. After the cement cured, the skin incision was sutured closed except where the plate protruded from the skull surface. The owl was given an i.m. injection of antibiotic (oxytetracycline amphoteric, 20 mg/kg) for prevention of bacterial infection. After each experiment, the owl was encased in a cylinder when it was returned to its individual recovery cage to prevent injury during recovery from anesthesia. The owl usually resumed feeding within 24 h after the last injection of Ketamine. If the owl failed to eat, a medical grade mixture of glucose and saline was subcutaneously injected until feeding resumed.

On the day of the first recording session, which took place a week after the placement of the head plate, another craniotomy of about 1.5 cm<sup>2</sup> in size was made through both layers of the skull. A small hole was made in the dura mater for insertion of electrodes. The depth of anesthesia was judged by touching the owl's toes and examining pupillary reflexes. A hot water heating pad was used to maintain the owl's body temperature. After an experimental session, the craniotomy was closed with a thin plastic sheet whose edges were cemented to the skull. The owl received oxytetracycline amphoteric (20 mg/kg) before going to the recovery cage. The owl was carefully monitored until it recovered well enough to fly.

All owls were bred in captivity at California Institute of Technology. All experiments were approved by the Institute Animal Care and Use Committee and conformed to international guidelines on the ethical use of animals and all efforts were made to minimize the number of animals used and their suffering.

### *Acoustic stimuli*

All acoustic stimuli were synthesized with a computer (Dimension XPS Pro200n, Dell). ITDs were computed on-line, while two digital attenuators (PA4, Tucker-Davis Technologies, Gainesville, FL, USA) set ILDs. Tonal and broadband stimuli (100 ms in duration, 5 ms linear rise/fall time, 500–12 000 Hz) were delivered once per second by an earphone assembly con-

sisting of a Knowles ED-1914 receiver as a sound source, a Knowles BF-1743 damped coupling assembly, and a calibrated Knowles 1939 microphone for monitoring sound pressure levels in the ear canal. The Knowles (Franklin Park, IL, USA) components were encased in an aluminum cylinder for insertion into the external meatus. The gaps between the cylinder and the ear canal were filled with silicon impression material (Gold Velvet, JKR Laboratories, Wichita, KS, USA). Before each experimental session the earphone assembly was calibrated *in situ*. The calibration data contained the amplitude and phase angles measured in steps of 500 Hz (500–12 000 Hz). The computer used these data to compensate for the frequency response of each earphone.

### *Drug injection and neural recording*

We used double-barrel glass electrodes to apply drugs to particular loci in the tonotopically organized NL. One barrel (outer diameter 1.0 mm, inner diameter 0.58 mm, with filament, borosilicate, World Precision Instruments, Sarasota, FL, USA) contained 1 M KCl (pH 7.4) for recording neuronal activities and the other (outer diameter 1.5 mm, inner diameter 0.86 mm, with filament, borosilicate, Sutter Instrument, Novato, CA, USA) contained drugs. The two barrels were bound together with a length of shrink tubing and were pulled with an electrode puller. The tip diameter was 6–13 μm for recording electrodes and 10–20 μm for drug barrels. A polyethylene tube connected the drug barrel to a Pneumatic Picopump (PV820, World Precision Instruments). Electrodes were positioned stereotaxically and advanced through the cerebellum to NL with a micro-drive.

Neural potentials through the recording electrode were amplified, monitored on an oscilloscope screen and with an audio monitor, and recorded in the computer. Once we recorded neuronal responses characteristic of NL such as the sensitivity to ITD, we kept the electrodes there while isolating OT or VLVp neurons. We recorded multiunit potentials as a function of ITD by setting the trigger level of the spike discriminator low and constant during data collection. These procedures gave rise to typical ITD curves.

We used GABA (Sigma, St. Louis, MO, USA) and a GABA<sub>A</sub> receptor agonist, muscimol (5-aminomethyl-3-hydroxyisoxazole, Sigma). They were used as a solution in saline with a concentration of 200 mM and 2 mM, respectively. We controlled the pressure (20–30 psi) and duration (2–6 s) of pulses necessary for ejecting 2–2.3 μl of solution. The total amount of administered drug (0.5 μg of muscimol) was similar to that reported in a previous study (Hikosaka and Wurtz, 1985). The pH of the solution was adjusted to 7.4. Drug injection sites in NL were identified in Cresyl Violet-stained sections.

We used neurons of the OT to study the effects of drug injection in NL on the response of higher-order neurons. Tectal neurons were selected for two reasons: they are sensitive to combinations of ITD and ILD and they are at the highest station in which the binaural cues are processed. To compare the effect of drugs, we chose neurons in the deep layers of the OT, because they tended to show sustained discharges in response to auditory stimuli and little spontaneous firing (Knudsen, 1984). For recording of single neurons in the OT Parylene-insulated tungsten microelectrodes (0.010" diameter, 5 MΩ at 1 kHz, A-M Systems Inc.) were advanced with a micro-drive (MM-3M, National Aperture, Salem, NH, USA). Neural impulses were amplified, monitored on an oscilloscope screen and with an audio monitor, and sent to the computer as TTL pulses for data acquisition. For histological verification of the location of recorded neurons, electrolytic lesions were made at the end of experiments by passing current (–3 μA, 20 s) and were visualized in Cresyl Violet-stained sections.

The data obtained from the OT were in the form of ITD and ILD tuning curves. ITD and ILD curves in all figures show the mean impulse counts from 10 stimulus repetitions and the standard deviations. In the external nucleus of ICx and OT, ITD curves obtained with broadband signals have one large peak (main peak) and smaller peaks (side peaks) flanking the main one. Frequency tuning curves were also obtained by plotting

mean discharge rates against tonal frequency (1000–12000 Hz, 500 Hz steps). These were measured with the neuron's most favorable combination of ITD and ILD for broadband noise.

RESULTS

*Effects of drugs on nucleus laminaris*

The NL is 3.5–3.8 mm in length, 3 mm in width, and 0.7 mm in thickness (Takahashi and Konishi, 1988). It is tonotopically organized and frequencies above 4 kHz occupy more than 60% of the nucleus (Carr and Konishi, 1990). We chose 6–8-kHz areas for both recording and drug injection, because they overlap little with both cochlear nuclei (NM and NA). We recorded multiunit potentials in NL in response to ITDs. As with single neurons, the ITD response of multiunits resembles a cosine function. The distance between the peaks or troughs of ITD curves corresponds to the inverse of the stimulus frequency. Injection of GABA into NL reduced the peaks of ITD curves as well as their modulation depth (peak–trough/peak) (Fig. 1, top row). Peaks started to decline right after GABA injection and gradually recovered over the next 30 min. We do not know the concentration of GABA to which NL neu-

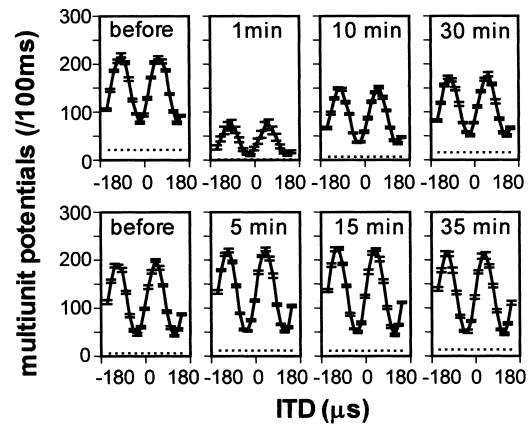


Fig. 1. Effects of GABA on multiunit potentials in NL. Injection of GABA reduced the rate of multiunit potentials to ITD at 6.5 kHz locus (upper row). The drug effects appeared within 1 min and waned within 30 min. The number of potentials is high, because all transient potentials were recorded with the trigger level set low. Multiunit ITD responses recorded simultaneously at the homologous site (same best frequency) in the contralateral NL did not change, indicating that GABA did not diffuse to the ipsilateral NM (lower row). The differences in recording time after drug injection between the rows are due to data processing time.

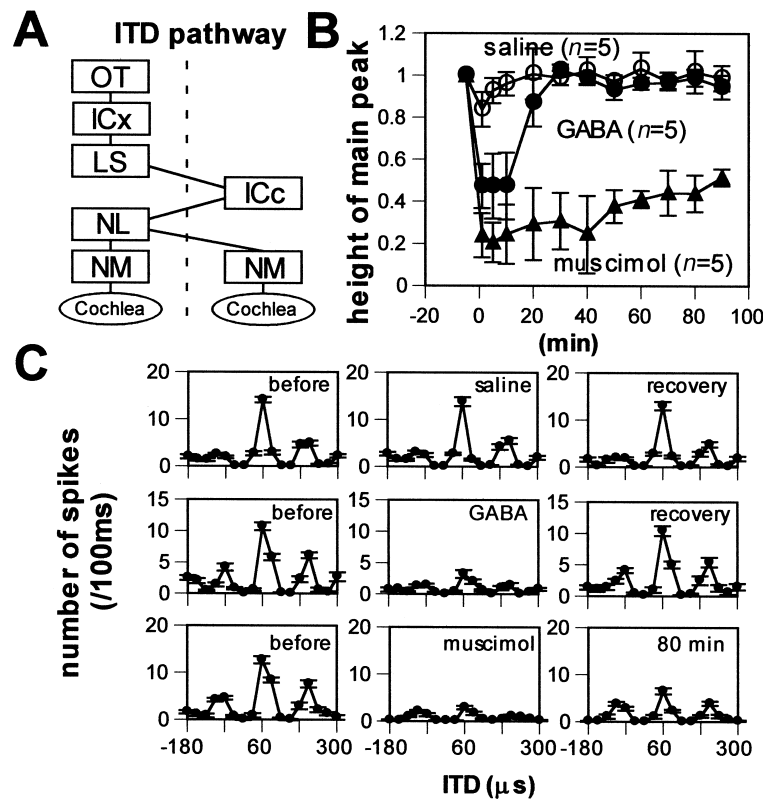


Fig. 2. Effects of drug injection in NL on neurons of OT. (A) ITD-processing pathway between NL and OT. ICc = core of the central nucleus of inferior colliculus. Drugs were injected in NL ipsilateral to OT. (B) The time course of drug effects. Monitoring single neurons in OT while drugs were injected in NL. Recovery from muscimol was much slower than that from GABA. Each curve shows the means of spike counts at the main peaks of five neurons and standard deviations of the means normalized to the means before drug injection. Symbols: open circle = saline, filled circle = GABA, filled triangle = muscimol. (C) Injection of GABA or muscimol into NL caused the ITD response of OT neurons to diminish. Examples of three neurons are shown. Each row indicates results from a single neuron. ITD curves connect the means of spike counts with standard deviations from 10 stimulus presentations. Abscissa: time after the end of drug injection to NL.

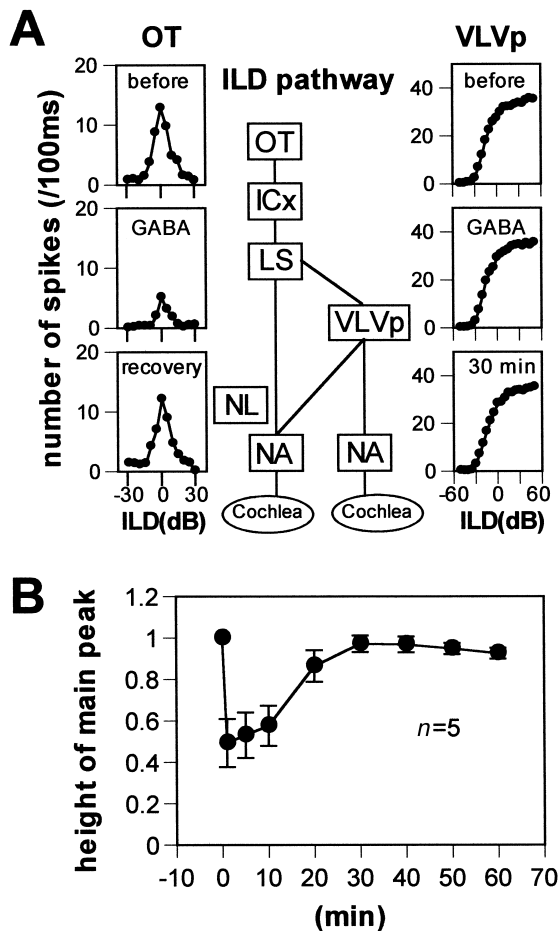


Fig. 3. Effects of GABA injection into NL on the ILD response of OT neurons. (A) Middle panel shows the connections of the ILD processing pathways. NA is the starting point of the pathway and VLVp is the first site where neurons show sensitivity to ILD. Injection of GABA into NL contralateral to VLVp had no effects on the response of neurons of VLVp to ILD (right panel), whereas it reduced both ITD and ILD responses of ipsilateral tectal neurons (left panel). One neuron from each area is shown as an example. 30 min indicates time after drug injection. (B) The time course of change in the ILD peak of five OT neurons (means and standard deviations) after drug injection to NL at time 0. The mean spike rates after drug injection are normalized to the mean spike rate before drug injection. The time course of change in the main ITD peak of OT neurons is shown in Fig. 2B.

rons were exposed, because the drug was not only taken up by neurons but also diffused into an unknown volume of tissue and body fluid.

The injection of GABA did not have any effects on the contralateral NL in which we made simultaneous recordings at the homologous tonotopic site. If GABA had spread into NM that receives GABAergic input, the drug would have affected the contralateral NL by reducing the NM input to that NL, which receives afferents from both NMs. We also measured the extent of drug effects within NL by measuring how the rate of multiunit potentials declined as a function of distance from the injection site. A distance corresponding to 2.0 kHz in the tonotopic map was the maximal extent of drug effects. This distance is approximately 1.5 mm between 5 and 7 kHz (Carr and Konishi, 1990).

### Effects of nucleus laminaris drug injection on tectal neurons

Ejection of GABA or muscimol in the 6–8-kHz zone of NL dramatically reduced the ITD response of neurons in the OT of the same side (Fig. 2B, C). The best frequency of tectal neurons is within this range, although they are broadly tuned to frequency. Higher-order neurons that are both ITD-sensitive and broadly frequency-tuned show one large peak (main peak) flanked by small peaks (side peaks) in their ITD curves. The drugs reduced both the main and side peaks, while the discharge rate at troughs remained at zero. All 10 neurons tested with either GABA or muscimol showed the same effects except that the time course of recovery differed between the two drugs. Both drugs caused the main peak to decline significantly within the first 5 min ( $P < 0.01$ , paired  $t$ -test), but its recovery to the original height took about 30 min with GABA and more than 90 min with muscimol (Fig. 2B). Injection of saline ( $n = 5$ ) alone had a small effect that was perhaps due to momentary lowering of tissue temperature or mechanical disturbance at the injection site. In all tectal neurons in which the effects of NL drug injection were studied, responses to ILDs also declined significantly ( $P < 0.01$ , paired  $t$ -test). This reduction is not due to direct interference with the ILD processing pathway, because the ILD response of VLVp neurons ( $n = 11$ ) contralateral to the injected NL did not change (Fig. 3). If the drug had diffused from NL to NA, it would have affected the excitatory response of neurons in the contralateral VLVp. However, while the drug in the NL affected the spike rate of tectal neurons, the selectivity of tectal neurons for ITD and ILD did not change. We used the width of ITD and ILD curves at half height as a measure of selectivity. The half-widths of ITD curves did not change (Mann–Whitney test,  $P = 0.75$ , 5 min and  $P = 0.35$ , 60 min after drug ejection). Similarly, the half-widths of ILD curves did not change (Mann–Whitney test,  $P = 0.40$ , 5 min and  $P = 0.75$ , 60 min after drug injection).

### DISCUSSION

The idea that inhibition might be involved in the detection of ITDs in both the medial superior olivary nucleus of mammals and the NL of birds came originally from the observation that the discharge level elicited by the least favorable ITD goes below the spontaneous level (Goldberg and Brown, 1969; Yin and Chan, 1990; Spitzer and Semple, 1995). Histochemical and neuropharmacological studies with slices have provided evidence for the presence of inhibitory transmitters such as GABA in the NL and glycine in the medial superior olive (Code et al., 1989; Carr et al., 1989; Code and Churchill, 1991; Carr and Boudreau, 1993; Lachica et al., 1994; Grothe and Sanes, 1993, 1994; Hyson et al., 1995; Funabiki et al., 1998; Yang et al., 1999). Despite these observations the action of inhibitory transmitters in these nuclei has not been studied *in vivo*. Injection of GABA or muscimol reduced the ITD responses of multi-

unit potentials in NL. The results reported above provide the first *in vivo* physiological evidence for GABA receptor-mediated inhibition in NL and are consistent with the presence of many GABAergic terminals on neurons in the owl's NL (Carr and Boudreau, 1993). This inhibition must be through GABA<sub>A</sub> receptors, because muscimol is an agonist specific for this receptor type (Chebib and Johnston, 1999). The effects of muscimol lasted longer than those of GABA. This may be due to differences in affinity to GABA receptors and uptake mechanisms. Muscimol is not a substrate for GABA transaminase and is transported inefficiently by GABA uptake systems (Fowler et al., 1983).

The functional role of GABA in NL is a subject of considerable interest, because the involvement of inhibition in the detection of ITDs would call for changes in the prevailing theory of binaural cross-correlation (Yin and Chan, 1988; Joris et al., 1998). According to recent studies of inhibition in slice preparations of NL, GABA reduces the size of excitatory postsynaptic potential (EPSP) by depolarizing the membrane. This process is thought to make the cell respond only to large EPSPs due to coincident arrival of signals from left and right afferent sources (Hyson et al., 1995; Funabiki et al., 1998). GABA also shortens the duration of EPSPs, presumably improving the resolution of coincident detection (Funabiki et al., 1998; Yang et al., 1999). The inhibition induced by repetitive stimulation of the superior olivary nucleus with which NL has reciprocal connections is long-lasting and lacks any temporal structure (Yang et al., 1999). This finding suggests that GABA receptor-mediated inhibition does not control short-term events such as phase-locked inhibition. These results are consistent with the idea that GABA receptor-mediated inhibition controls only the gain of the coincidence detectors (Lachica et al., 1994; Peña et al., 1996; Yang et al., 1999). The ultimate answer to this question must come from the study of single neurons *in vivo*.

Injection of GABA in NL reduced the amplitude of ITD curves of OT neurons. Takahashi et al. (1984) showed that partial inactivation of NM or NA affected

only ITD or ILD, respectively, but not both. This finding led to the idea of independent processing of the two cues. The authors also observed that the amplitude of both ITD and ILD curves decline when either cochlear nucleus was partially inactivated. The significance of this observation escaped the authors' attention. Our results are consistent with theirs in that injection of GABA into NL reduced the amplitude of both ITD and ILD curves in the OT. We went further to show that the effect on ILD curves was not due to the drug spreading into the intensity processing pathways. The question is why the two pathways influence each other, if they are independent. The interaction between ITD and ILD occurs not between the pathways but within the neurons that receive input from both of them. We now know that the sensitivity to combinations of ITD and ILD is due to multiplication of inputs from the two pathways (Peña and Konishi, 2001). Thus, a reduced input from one pathway can lead to a reduced output, even though the other pathway is unaffected. OT neurons respond to the manipulation of one input like ICx neurons (Albeck and Konishi, 1995; Saberi et al., 1998). OT neurons receive input that is a result of multiplication and other non-linear processes. Nevertheless, it is possible to show that the response of OT neurons to ITD-ILD pairs consists of ITD and ILD components. Changing the amplitude of ITD input does not affect the selectivity of OT neurons for ITD or ILD. The response amplitude of the same neurons for combinations of ITD-ILD does, however, vary with the amplitude of ITD input. This explanation accounts for the observed results.

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