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Two crossed axonal projections contribute to binaural unmasking of frequency-following responses in rat inferior colliculus

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Abstract

Frequency-following responses (FFRs) are sustained potentials based on phase-locked neural activities elicited by low- to medium-frequency periodical sound waveforms. Human brainstem FFRs, which are able to encode some critical acoustic features of speech, can be unmasked by binaural processing. However, the underlying unmasking mechanisms have not previously been reported. In rats, most neurons in the inferior colliculus (IC) exhibit binaural responses which are affected by axonal projections from both the contralateral dorsal nucleus of the lateral lemniscus (DNLL) and the contralateral IC. The present study investigated whether the contralateral DNLL and the contralateral IC modulate binaural unmasking of FFRs recorded in the rat IC. The results show that IC FFRs to the rat pain call (chatter) were enhanced by local injection of the excitatory glutamate receptor antagonist kynurenic acid (KYNA) into the contralateral DNLL but were reduced by KYNA injection into the contralateral IC. Introducing a disparity between the interaural time difference (ITD) of the FFR-eliciting chatter and the ITD of the masking noise enhanced IC FFRs. Moreover, the ITD-disparity-induced FFR enhancement was weakened by injection of KYNA into either the contralateral DNLL or the contralateral IC when the ipsilateral chatter preceded the contralateral chatter. Thus, binaural hearing can improve IC FFRs against noise masking. More importantly, both inhibitory projections from the contralateral DNLL and excitatory projections from the contralateral IC modulate IC FFRs and play a role in forming binaural unmasking of IC FFRs.

Introduction

Frequency-following responses (FFRs) are sustained potentials based on precisely phase-locked responses to low- to medium-frequency periodical sound waveforms (Marsh *et al.*, 1970; Smith *et al.*, 1975). Human scalp-recorded FFRs reflect activities of brainstem neurons and are capable of encoding both spectra (Krishnan, 2002; Russo *et al.*, 2004) and pitch contours (Hall, 1979; Krishnan *et al.*, 2004) of speech. Interestingly, human FFRs can be modulated by both language experience (Galbraith *et al.*, 2004; Krishnan *et al.*, 2005; Xu *et al.*, 2006; Swaminathan *et al.*, 2008) and selective attention (Galbraith *et al.*, 2003).

Due to the presence of extraneous noises under everyday environments, several salient features of acoustic signals, particularly for life-threatening acoustic signals, such as predator calls (Hendrie *et al.*, 1998) and species-specific pain calls (Dennis & Melzack, 1983), must be precisely retained in neural coding by certain unmasking mechanisms. It is well known that signal detection against interfering background noise is improved by binaural hearing (e.g. Hirsh, 1948). Indeed, both binaural unmasking and spatial unmasking have been demonstrated in both humans (Saberi *et al.*, 1991; Gilkey & Good, 1995; Shinn-Cunningham *et al.*, 2001) and animals (Hine *et al.*, 1994; Dent *et al.*, 1997). In particular, human brainstem FFRs can also be unmasked by binaural processing (Wilson & Krishnan, 2005).

Although the corresponding physiological correlates of binaural/spatial unmasking have been found in the auditory midbrain, inferior colliculus (IC), of guinea-pigs (e.g. Caird *et al.*, 1991; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Palmer *et al.*, 2000), chinchillas (e.g. Mandava *et al.*, 1996), cats (e.g. Lane & Delgutte, 2005) and frogs (e.g. Ratnam & Feng, 1998; Lin & Feng, 2001, 2003), the neural pathways that are critically responsible for the formation of binaural unmasking of neural activity in the IC remain to be determined.

Most neurons in the IC exhibit binaural responses, which can be shaped by GABAergic axonal projections from the contralateral dorsal nucleus of the lateral lemniscus (DNLL) (Burger & Pollak, 2001; Faingold *et al.*, 1993; Kelly & Li, 1997; Kidd & Kelly, 1996; Li & Kelly, 1992; Van Adel *et al.*, 1999; Zhang *et al.*, 1998; for a review see Li & Yue, 2002). The rat IC, which has a cytoarchitecture similar to that of the cat IC (Loftus *et al.*, 2008), also receives crossed axonal projections from its counterpart, the contralateral IC (Irvine, 1986; González-Hernández *et al.*, 1996; Saint Marie, 1996;

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Zhang *et al.*, 1998; Hernández *et al.*, 2006) with both divergent and point-to-point wiring patterns (Malmierca *et al.*, 2009). The intercollicular commissure plays a role in modulating both binaural responses and frequency-response areas in the IC (Malmierca *et al.*, 2003, 2005). However, it is unknown whether inputs from the contralateral DNLL and/or those from the contralateral IC affect binaural unmasking in the IC.

To provide an initial understanding of why FFRs recorded in humans, which are based on synchronized activities of a sufficiently large population of neurons in the auditory midbrain, can be unmasked by binaural hearing, we used here a segment of the rat tail-pain chatter that consists of harmonics (Jourdan *et al.*, 1995) to investigate: (i) whether the chatter-evoked FFRs recorded in the rat IC are affected by binaural processing and even unmasked by introducing a disparity between the interaural time difference (ITD) of the chatter and that of the masking noise, and (ii) whether chemical blockade of either the contralateral DNLL or the contralateral IC by kynurenic acid (KYNA), a broad-spectrum glutamate receptor antagonist, affects FFRs and/or binaural unmasking of FFRs in the IC.

Materials and methods

Animal preparation

Forty-eight young-adult male Sprague–Dawley rats (age 10–12 weeks, weight 300–350 g) were used and treated in accordance with the Guidelines of the Beijing Laboratory Animal Center and the Policies on the Use of Animals and Humans in Neuroscience Research approved by the Society for Neuroscience (2006). Procedures of this study were approved by the Committee for Protecting Human and Animal Subjects, the Department of Psychology at Peking University. Rats were divided into four structure/injection-agent groups: (i) DNLL/KYNA (n = 14), (ii) DNLL/Locke's solution (n = 10), (iii) IC/KYNA (n = 14), and (iv) IC/Locke's solution (n = 10).

Rats were anaesthetized with 10% chloral hydrate (400 mg/kg, i.p.) and the state of anaesthesia was maintained throughout the experiment by supplemental injection of the same anaesthetic. Stainless steel recording electrodes (10–20 kΩ) insulated by a silicon tube (0.3 mm in diameter) except at the 0.25-mm-diameter tip (Zheng *et al.*, 2008) were aimed at the IC on either side in all the 48 rats and injection guide cannulae (C317G guide cannula; Plastics One Inc., Roanoak, VA, USA) were aimed at either the contralateral DNLL or the contralateral IC (relative to the recorded IC). Based on the stereotaxic coordinates of Paxinos & Watson (1997) and referenced to Bregma, IC coordinates were: AP, −8.8 mm; ML, ± 1.5 mm; DV, −4.5 to −5.0 mm, and DNLL coordinates were: AP, −8.3 to −8.7 mm; ML, ± 2.9 mm; DV, −6.5 to −6.8 mm.

Acoustic stimulation and recording

A train of tail-pain chatter (simply termed 'chatter') was recorded from one rat in response to tail-clamping pain in a soundproof chamber and digitized at 44.1-kHz sampling rate and 16-bit resolution. A 150-ms stimulus section without any amplitude-modulation or frequency-modulation was isolated from one selected chatter burst and tapered with 5-ms linear onset/offset ramps. The spectrum of the chatter shows a fundamental frequency (F0) at 2.1 kHz and two harmonics at 4.2 (h2) and 6.3 kHz (h3), respectively. The relative size of each of the three frequency components has been reported in our previous study (Du *et al.*, 2009), showing that F0 and h2 of the chatter are approximately equal in amplitude and h3 is about 16 dB lower in amplitude.

The masker was a burst of broadband white noise (0–10 kHz) with a duration of 750 ms (including 5-ms linear onset/offset ramps). It was started 500 ms before the onset of the chatter.

All sound waves were processed by a TDT System II (Tucker-Davis Technologies, Alachua, FL, USA), and presented through two ED1 earphones. A 12-cm TDT sound-delivery rubber tube was connected to each ED1 earphone and inserted into rat's ear canal. Both chatter in quiet and chatter in noise at the tube end were calibrated using a Larson Davis Audiometer Calibration and Electroacoustic Testing System (AUDit™ and System 824; Larson Davis, Provo, UT, USA). The sound-pressure level (SPL) of chatter in quiet was 59 dB when each earphone played alone. Under conditions with masking noise presentations, the chatter intensity was held constant at this level while the whole-spectrum intensity of the white noise was adjusted to produce two signal-to-noise ratios (SNRs): −4 and 4 dB.

Neural potentials were recorded in a sound-attenuating chamber, amplified 1000-fold, bandpass filtered at 200–10 000 Hz, and averaged 50 times per condition. Online recordings were processed with TDT Biosig software, finally digitized at 16 kHz and stored on disk for offline analysis.

Drug injection

Drug administration was made through the guide cannula which was connected to a 5.0-μL micro-syringe via polyethylene tubing (inner diameter: 0.38 mm, outer diameter: 1.09 mm; Clay Adams, division of Becton and Dickinson Company, Parsippany, NJ, USA). Either the broad-spectrum antagonist KYNA (2 mM in Locke's solution; Sigma-Aldrich, St Louis, MO, USA) or Locke's solution was injected slowly into the contralateral DNLL (1.0 μL) or the contralateral IC (2.0 μL) over a period of about 1 min. Recording started 10 min after injection.

Experimental procedures

Before injection, rats were first adapted to the chatter presented to both ears for 10 min, then the following stimuli were presented: (i) monaural chatter (ipsilateral, I; contralateral, C) in quiet, (ii) binaural chatter in quiet with the following ITDs: −0.1 ms (ipsilateral chatter leading, I/C), 0 ms (binaurally simultaneous, ST), and +0.1 ms (contralateral chatter leading, C/I) and (iii) binaural chatter in interaurally correlated noise.

Under conditions with co-presentation of masking noise, when the ITD for chatter was −0.1 or +0.1 ms, and the ITD for noise was −0.1, 0 or +0.1 ms, there were three absolute ITD disparities between signal and noise ($|ITD_{S+N}|$): 0 (no ITD disparity), 0.1 (smaller ITD disparity) and 0.2 ms (larger ITD disparity). Note that the ITD value of 0.1 ms was shorter than the maximum ITD due to the head size of rats (0.13–0.16 ms, Koka *et al.*, 2008). Thus we assume that for awake rats when $|ITD_{S+N}|$ is zero, no position separation is perceived between signal image and noise image; when $|ITD_{S+N}|$ is 0.1 ms, signal is perceived at one ear and noise is perceived at the centre of the head (smaller perceived signal/noise separation); when the $|ITD_{S+N}|$ is 0.2 ms, signal is perceived at one ear and noise is perceived at the other ear (larger perceived signal/noise separation).

The onset-to-onset inter-stimulus interval (ISI) was 800 ms for signals presented in quiet and 1000 ms for signals presented in noise. FFRs in quiet were recorded for a duration of 200 ms beginning at signal onset, while FFRs in noise were recorded for a duration of 800 ms

beginning at noise onset. Recordings were carried out before and after microinjection of KYNA or Locke's solution for each of the groups.

Data analyses

For acoustically evoked potentials recorded in quiet, a 1000-Hz low-pass filter was used to smooth the waveform and the latency of the first positive onset peak was determined. A fast Fourier transform (FFT) was performed for each unfiltered FFR in quiet. The spectral peak amplitude of a 100-Hz-wide frequency band centred at 2.1 kHz was determined as the FFR F0 amplitude.

For acoustically evoked potentials recorded in noise, FFT was performed during a period from the chatter onset to 15 ms after the chatter offset, and the spectral peak amplitude of a 100-Hz-wide band centred at 2.1 kHz was determined and labelled as FFR F0 amplitude of signal in noise (AMP_{s+n}). The mean spectral amplitude of two 200-Hz-wide sidebands centred at 1.95 and 2.25 kHz was defined as amplitude of noise (AMP_n). The response signal-to-noise ratio (rSNR) was defined as AMP_{s+n}/AMP_n.

The unmasking index (UI), which was used to evaluate the effect of specific ITD disparity between signal and masker ($|ITD_{S+N}|$) on FFR efficacy (represented by rSNR), was then calculated as a mean proportion of change in rSNR (rSNR when $|ITD_{S+N}| = 0$ was used as baseline) under two stimulus SNRs (sSNRs: −4 and 4 dB):

$$\mathrm{UI}(\%) = 100\% \times \frac{\frac{\mathrm{rSNR}(-4,\mathrm{N})-\mathrm{rSNR}(-4,0)}{\mathrm{rSNR}(-4,0)} + \frac{\mathrm{rSNR}(4,\mathrm{N})-\mathrm{rSNR}(4,0)}{\mathrm{rSNR}(4,0)}}{2}$$

where '−4' and '4' represent the stimulus SNR of −4 and +4 dB, respectively, '0' represents zero ITD disparity ($|ITD_{S+N}| = 0$) and 'N' represents a specific ITD disparity (0.1 or 0.2 ms). 'rSNR(−4,0)', for example, represents the response SNR when stimulus SNR was −4 dB and the zero ITD disparity was introduced.

Statistical analyses

Statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Within-subjects, repeated-measures analyses of variance (ANOVAs) were conducted to assess differences between conditions. The null hypothesis rejection level was set at 0.05.

Histology

When all recordings were finished, rats were killed with an overdose of chloral hydrate. Lesion marks were made via the recording electrodes by an anodal DC current (500 μA for 10 s). Brains were stored in 10% formalin with 30% sucrose, and then sectioned at 40 μm in the frontal plane in a cryostat (−20°C). Sections were examined to determine locations of recording electrodes and injection cannulae.

Results

According to histological examination (Fig. 1), electrodes were located precisely within the IC area in 45 of the 48 rats. Injection cannulae were located precisely within the DNLL area in 21 of 24 rats, and within the IC area in 21 of 24 rats. Rats with either misplaced recording electrodes or misplaced injection cannulae were removed from data analyses, thus, descriptions and statistical analyses here were based on the data from 42 rats (13 in the DNLL/KYNA group, 8 in the DNLL/Locke's group, 12 in the IC/KYNA group and 9 in the IC/Locke's group).

Monaural and binaural FFRs in quiet

When the noise masker was not presented, evoked field potentials to the chatter presented at the contralateral ear exhibited much larger onset responses (Fig. 2A) than those to the chatter at the ipsilateral ear (Fig. 2B). The mean latency of the first positive peak of the onset response to the chatter at the contralateral ear was 6.29 ms ($n = 42$, SD = 0.46 ms). Fast Fourier spectral analyses of field-potential waveforms to the chatter presented at either the contralateral or the ipsilateral ear clearly revealed the F0 and h2 components in all of the 42 rats (Fig. 2C and D), but the h3 component was not distinct and found only in 7 rats. These results indicate that only the fundamental frequency and the h2 of the rat's pain call could be precisely coded in the rat IC. Thus, the FFR is a 'distorted' version of the input signal with weakened representations of high-frequency components.

Binaural FFRs were investigated by presenting the signal at both ears and manipulating the ITD. Figure 3 shows mean normalized chatter–F0 amplitudes under various monaural/binaural stimulation conditions across all the 42 rats before the injection manipulation. Presenting signal only at the contralateral ear (Condition C) served as the baseline condition (F0 amplitude = 1) for normalization.

A within-subjects, repeated-measures ANOVA indicates significantly different F0 amplitudes across stimulation conditions ($F_{4,38} = 126.842$, $P < 0.001$). Pairwise comparisons show that: (i) F0 amplitude under Condition I (ipsilateral only) did not differ significantly from that under Condition C (contralateral only); (ii) F0 amplitude under each of the three binaural conditions (I/C, ipsilateral chatter leading; ST, binaurally simultaneous chatters; and C/I, contralateral chatter leading) was significantly higher than that under each of the two monaural conditions (all $P < 0.01$ except that the P value for the comparison of Condition C/I and I is 0.015), indicating a remarkable binaural integration effect; (iii) F0 amplitude under Condition I/C and that under Condition ST were significantly larger than that under Condition C/I (both $P < 0.001$), but the F0 amplitude under Condition I/C was not significantly different from that under Condition ST, indicating an effect of ipsilateral-input facilitation for binaural FFRs.

Effects of blocking DNLL or IC on FFRs in quiet

Figure 4 shows normalized chatter–F0 amplitudes of FFRs in quiet under various monaural/binaural stimulation conditions, before and after either KYNA or Locke's solution was injected into the contralateral DNLL (Fig. 4A and B) or the contralateral IC (Fig. 4C and D). The chatter–F0 amplitude under Condition C before injection served as the baseline condition (F0 amplitude = 1) for normalization.

For the DNLL/KYNA group (Fig. 4A), a 2 (testing time: pre-injection, post-injection) by 5 (stimulation condition) within-subjects, repeated-measures ANOVA shows that F0 amplitude significantly increased after KYNA injection ($F_{1,12} = 6.814$, $P < 0.05$), and the main effect of stimulation condition was significant ($F_{4,9} = 96.088$, $P < 0.001$), but the interaction between testing time and stimulation condition was not significant ($F_{4,9} = 0.528$, $P > 0.05$). This result suggests that blockade of glutamate transmissions in the contralateral DNLL by KYNA generally enhanced IC FFRs across stimulation conditions.

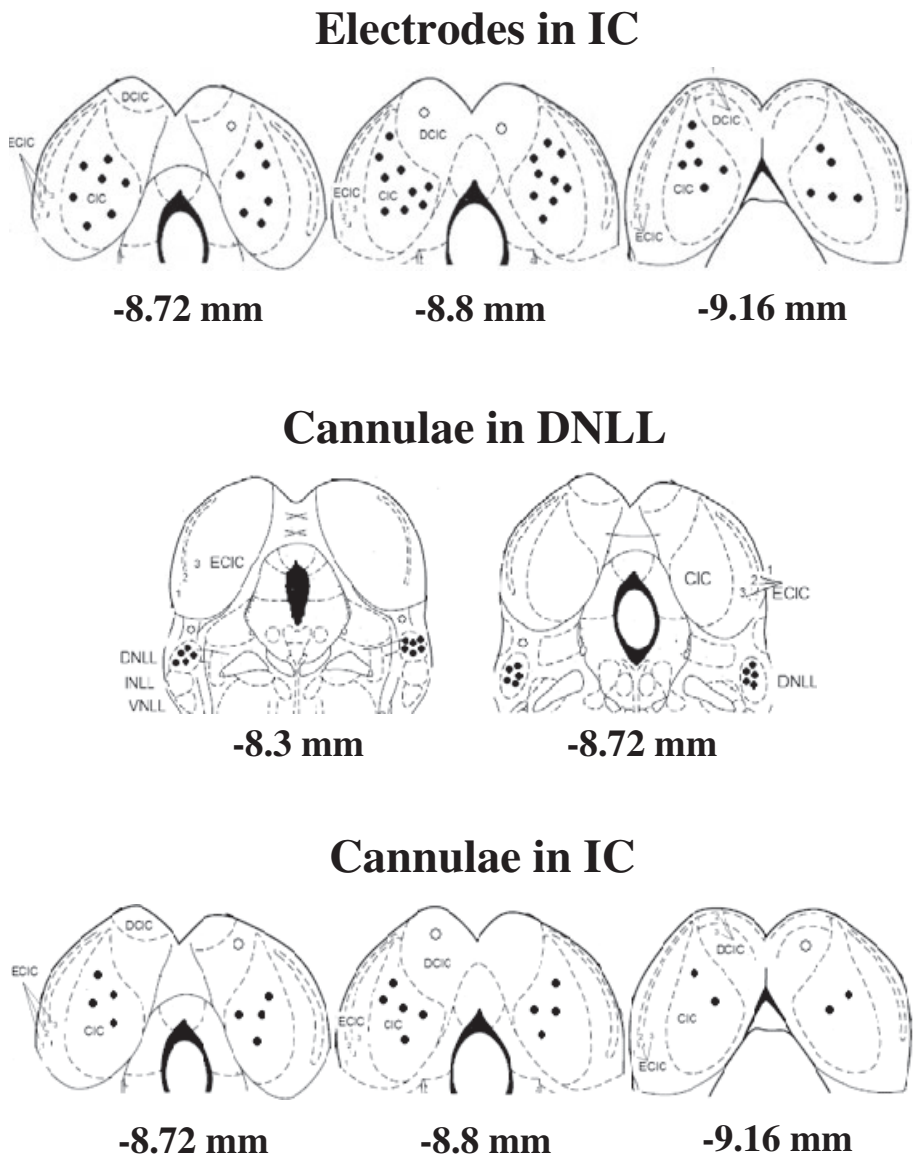

FIG. 1. Locations of recording electrodes and injection cannulae in all 48 rats. Electrodes were located precisely within the inferior colliculus (IC) area in 45 of 48 rats (filled circles), and injection cannulae were located precisely within the dorsal nucleus of the lateral lemniscus (DNLL) area in 21 of 24 rats, and within the IC area in 21 of 24 rats (filled circles). Incorrect locations of electrodes and cannulae are shown by open circles.

For the IC/KYNA group (Fig. 4C), a within-subjects, repeated-measures ANOVA reveals that F0 amplitude significantly decreased after KYNA injection ($F_{1,11} = 18.303$, $P < 0.01$), and the main effect of stimulation condition was significant ($F_{4,8} = 74.447$, $P < 0.001$), but the interaction between testing time and stimulation condition was not significant ($F_{4,8} = 0.596$, $P > 0.05$). This result suggests that blockade of glutamate transmissions in the contralateral IC by KYNA generally weakened IC FFRs across stimulation conditions.

By contrast, for the other two groups with Locke's solution injection (Fig. 4B and D), repeated-measures ANOVAs indicate that neither the main effect of testing time nor the interaction between testing time and stimulation condition was significant (all $P > 0.05$), but the main effect of stimulation condition was significant (all $P < 0.01$). Thus, injection of Locke's solution into either the contralateral DNLL or the contralateral IC did not affect FFRs recorded in the IC.

Binaural unmasking of FFRs

Figure 5 shows relative rSNRs of IC FFRs when the chatter was co-presented with white noise before injection manipulations with the ipsilateral chatter either leading or lagging behind the contralateral one by 0.1 ms. Clearly, when the ipsilateral chatter led the contralateral one, compared with the condition without ITD disparity ($|ITD_{S+N}| = 0$ ms), introducing an ITD disparity (0.1 or 0.2 ms) markedly enhanced the rSNR. However, when the leading ear for chatter changed to the contralateral ear, the ITD-disparity-induced enhancement of rSNR decreased remarkably.

The binaural unmasking effect of ITD disparity between the chatter and noise masker was also quantified over the mean UIs under different ITD disparity conditions. UIs are displayed separately when the ipsilateral chatter either led (Fig. 6A) or lagged behind (Fig. 6B) the contralateral chatter. We found that the FFR SNRs significantly increased with increasing ITD disparity between

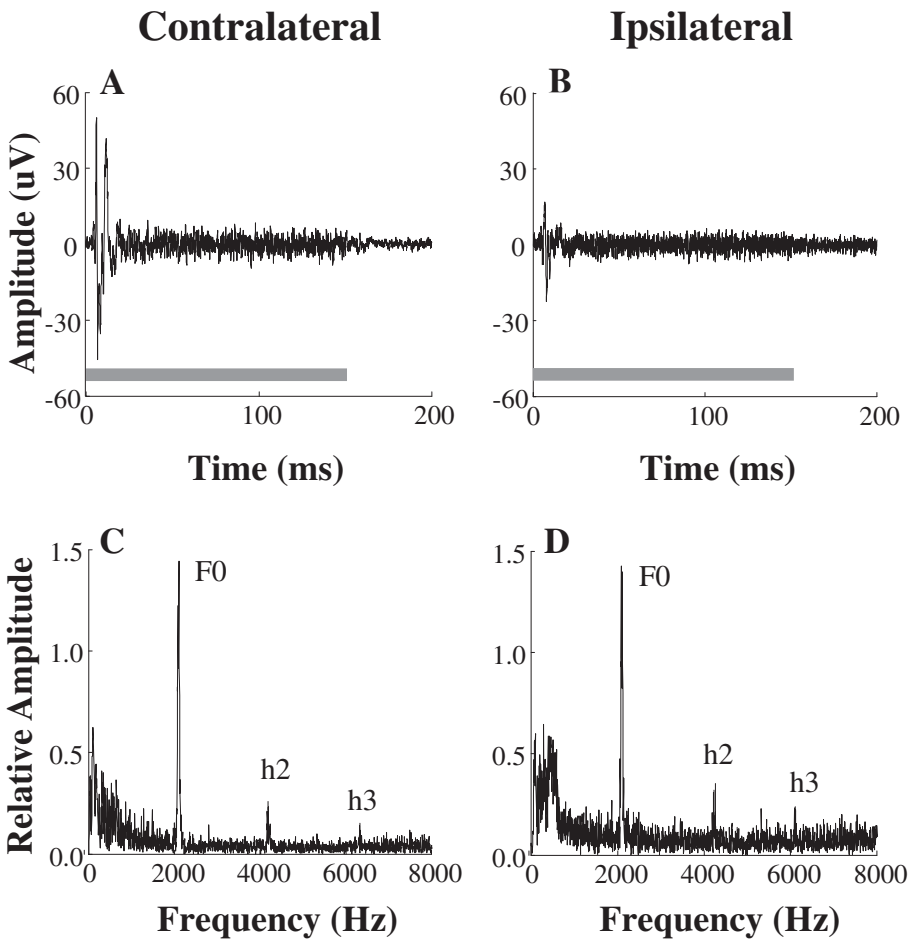

FIG. 2. Typical response waveforms to chatter (A and B) and fast Fourier spectral analyses of IC FFRs (C and D). Note that the recording site contralateral to the stimulated ear (A and C) exhibits a much larger onset-evoked potential than the site ipsilateral to the stimulated ear (B and D), but contralateral FFRs and ipsilateral FFRs exhibit similar F0 and h2 amplitudes. The horizontal bar in A and B represents the duration of the chatter stimulus.

the signal and noise ($F_{4,38} = 125.152$, $P < 0.001$), which was shown by the more positive UI under the larger ITD disparity condition (the UI value is zero when ITD disparity is zero), regardless of whether the chatter was ipsilateral-ear leading or contralateral-ear leading. Pairwise comparisons reveal that (i) even 0.1-ms ITD disparity led to significant enhancement of rSNR regardless of the chatter-ITD (both $P < 0.01$); (ii) 0.2-ms ITD disparity induced remarkably larger rSNR enhancement than 0.1-ms ITD disparity regardless of the chatter-ITD (both $P < 0.001$) and (iii) the same ITD disparity induced significantly larger improvement of rSNR when the chatter was ipsilateral-ear leading than contralateral-ear leading (both $P < 0.01$). These results indicate that FFRs in the rat IC can be improved by introducing an ITD disparity between the chatter and the noise masker, and the binaural unmasking of FFRs exhibits a marked advantage when the signal at the ipsilateral ear leads that at the contralateral ear.

Effects of blocking DNLL or IC on binaural unmasking of FFRs

The contribution of the contralateral DNLL or that of the contralateral IC to binaural unmasking of FFRs was examined by injecting either KYNA (Figs 7A and C, and 8A and C) or Locke's solution (Figs 7B and D, and 8B and D) into either of the two structures. The results are shown for conditions when chatter at the ipsilateral ear led the contralateral ear (Fig. 7) or chatter at the contralateral ear led the ipsilateral ear (Fig. 8).

When the ipsilateral chatter led, for the DNLL/KYNA group (Fig. 7A), a 2 (testing time: pre-injection, post-injection) by 2 ($|ITD_{S+N}|$) within-subjects, repeated-measures ANOVA shows that the main effect of testing time was significant ($F_{1,12} = 13.286$, $P < 0.05$), the main effect of $|ITD_{S+N}|$ condition was significant ($F_{1,12} = 29.797$, $P < 0.001$), and the interaction between time and $|ITD_{S+N}|$ was significant ($F_{1,12} = 5.598$, $P < 0.05$). Additional paired-sample *t*-tests show that blockade of glutamate receptors in the contralateral DNLL significantly reduced the binaural unmasking effect of FFRs under both 0.1-ms ($P < 0.05$) and 0.2-ms ($P < 0.01$) $|ITD_{S+N}|$ conditions.

Repeated-measures ANOVA for the IC/KYNA group (Fig. 7C) shows that the main effect of testing time was significant ($F_{1,11} = 28.650$, $P < 0.001$), the main effect of $|ITD_{S+N}|$ condition was significant ($F_{1,11} = 129.840$, $P < 0.001$), but the interaction between testing time and $|ITD_{S+N}|$ was not significant ($F_{1,11} = 1.639$, $P > 0.05$). Additional paired-sample *t*-tests confirm that blocking the glutamate receptors in the contralateral IC significantly reduced the binaural unmasking effect of IC FFRs under both $|ITD_{S+N}|$ conditions (both $P < 0.01$).

By contrast, for the two Locke's solution groups under ipsilateral chatter-led conditions, (Fig. 7B and D), separate repeated-measures ANOVA shows that the main effect of $|ITD_{S+N}|$ condition was

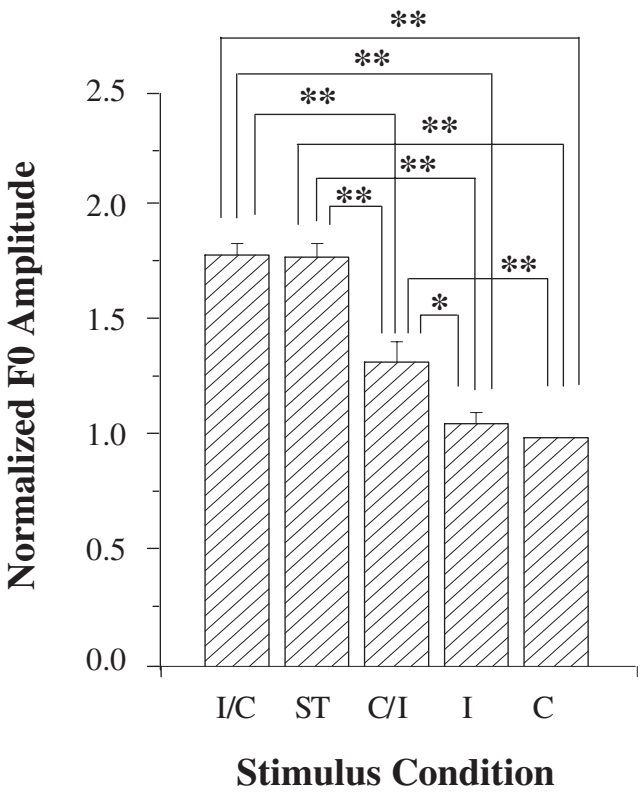

FIG. 3. Monaural and binaural IC FFRs. Mean normalized F0 spectral amplitudes in FFRs under various stimulation conditions are shown for 42 rats before injection manipulations. F0 amplitude evoked by contralateral stimulation only (C) served as the baseline condition (amplitude = 1) for amplitude normalization. Error bars in this and the following figures represent the standard error of the mean (SEM). I/C, binaural stimulation with ipsilateral (relative to recording site) chatter leading contralateral chatter; ST, simultaneous binaural stimulation; C/I, contralateral chatter leading ipsilateral chatter; I, chatter at ipsilateral ear only; C, chatter at contralateral ear only. $^{**}P < 0.01$, $^{*}P < 0.05$, repeated-measures ANOVA.

significant (both $P < 0.01$), the main effect of testing time was not significant (both $P > 0.05$), and the interaction between testing time and $|ITD_{S+N}|$ was not significant (both $P > 0.05$).

When the contralateral chatter led, for the two KYNA and the two Locke's solution groups (Fig. 8A–D), separate 2 (testing time) by 2 ($|ITD_{S+N}|$) repeated-measures ANOVA shows that the main effect of $|ITD_{S+N}|$ condition was significant (all $P < 0.05$), the main effect of testing time was not significant (all $P > 0.05$), and the interaction between testing time and $|ITD_{S+N}|$ was also not significant (all $P > 0.05$).

Therefore, both inputs from the contralateral DNLL and the contralateral IC contributed to the binaural unmasking effect of FFRs in rat auditory midbrain. However, these modulations of binaural unmasking effect occurred only when the signal at the ipsilateral ear led the contralateral ear.

Discussion

Latencies to the chatter presented at the contralateral ear

In our previous study using the same type of electrodes (Du *et al.*, 2009), for the onset response to the chatter presented at the contralateral ear, the latency of the first positive peak recorded in the lateral nucleus of the amygdala was 8.0 ms. By contrast, in the present study, the latency of the first positive peak of the onset response recorded in the IC to the chatter at the contralateral ear was 6.3 ms. This latency value is within both the latency range (4–30 ms) of the first spike to clicks obtained in the young Long-Evans rat central nucleus of the IC as reported by Irvine *et al.* (1995) and the latency range (6.2–77.2 ms) of the first spike to tone bursts obtained in the young Fischer 344 rat central nucleus of the IC as reported by Palombi & Caspary (1996). Thus, although a high degree of spatial resolution of the intracranial recordings used in the present study was not particularly emphasized, the response-latency results indicate that the acoustically evoked responses with sufficiently large amplitude recorded with electrodes inside the IC were neural activities generated within the IC.

Profile of major results

The results of the present study show that in anaesthetized rats, a segment of species-specific pain call (rat chatter), presented either monaurally or binaurally, was able to elicit marked FFRs in the rat IC. In addition, noise masking of IC FFRs to the chatter can be reduced significantly by binaural processing. More importantly, KYNA blocking of either the contralateral DNLL or the contralateral IC weakened binaural unmasking of IC FFRs, even though the effects of blocking these two contralateral structures under quiet conditions were opposite: blocking of the contralateral DNLL generally enhanced FFRs while blocking of the contralateral IC generally reduced FFRs. The results suggest that binaural unmasking of FFRs recorded in the IC depends on the two contralateral inputs whose unmasking mechanisms are different.

Contribution of EE neurons to FFRs in the IC

In rats, previous studies (e.g. Kelly *et al.*, 1991) have shown that the majority of auditory neurons in the IC are predominantly excited by stimuli at the contralateral ear and inhibited by stimuli at the ipsilateral ear, forming the so-called 'EI' neurons. Also, a small portion (about 20%) of IC neurons in rats are excited by stimuli at either ear (Kelly *et al.*, 1991), forming the so-called 'EE' neurons, which are sensitive to ITD. The remaining neurons are only excited by contralateral stimuli, forming the so-called 'EO' neurons. It is expected that FFRs to contralateral stimulation would be stronger than FFRs to ipsilateral stimulation, because contralateral stimulation drives all the three types of neurons (EE, EI, EO) in the IC but ipsilateral stimulation drives EE neurons only. However, the results of the present study show that when the noise masker was not present, although the chatter at the contralateral ear evoked much larger onset responses than the chatter at the ipsilateral ear, the normalized amplitude of IC FFRs to the contralateral chatter was similar to that to the ipsilateral chatter, without showing a marked contralateral dominance in eliciting IC FFRs. Moreover, IC FFRs to binaural-chatter stimulation exhibit a feature of ipsilateral predominance: FFRs were markedly stronger when the ipsilateral chatter either led or started simultaneously with the contralateral chatter than when the ipsilateral chatter lagged behind the contralateral chatter. These results suggest that EE neurons in the IC provide the major contribution to binaural FFRs.

Binaural unmasking of IC FFRs

The present study shows for the first time that in rats with noise masker present, IC FFRs to the signal were improved by introducing an ITD disparity between the signal and the noise masker. The results

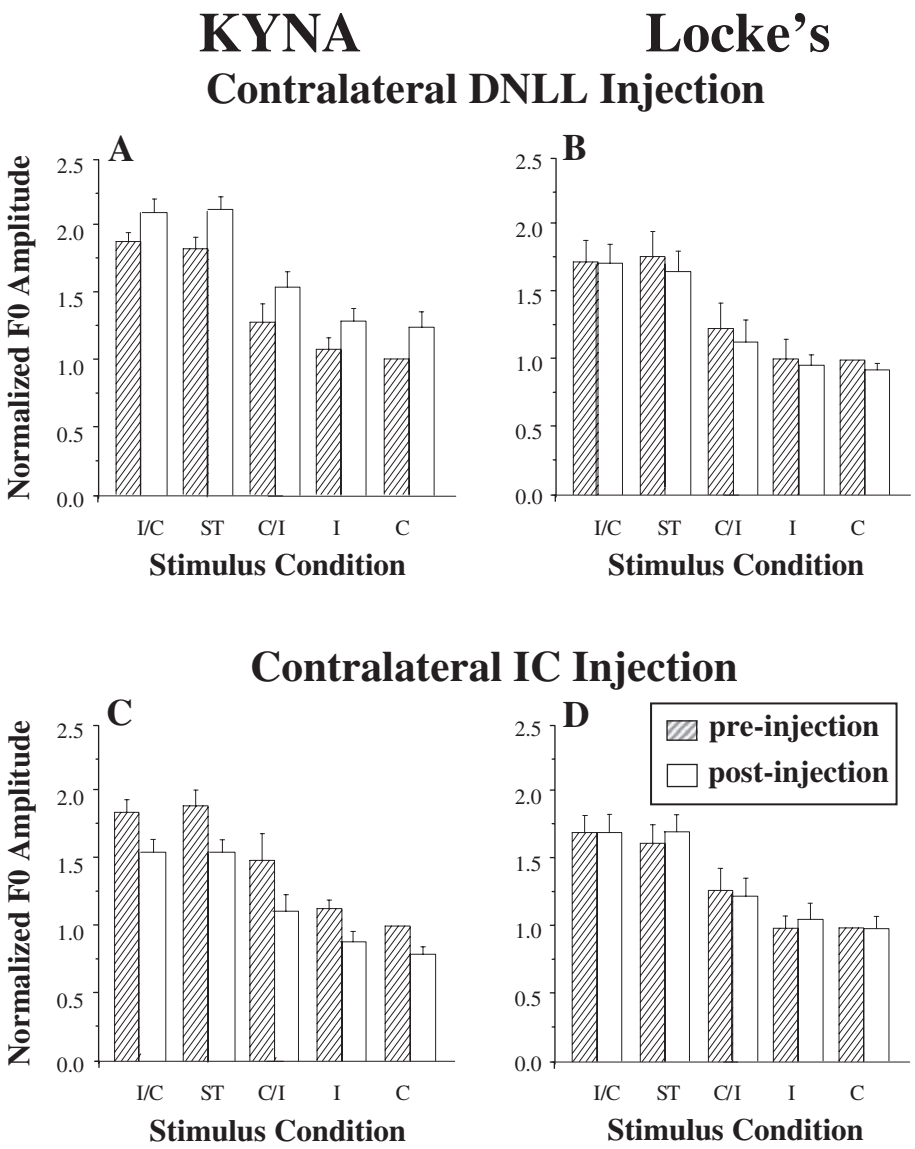

FIG. 4. Effects of blocking of the contralateral DNLL or the contralateral IC on IC FFRs. Normalized F0 amplitudes of FFRs under various monaural/binaural stimulation conditions are shown before (hatched bars) and after (open bars) either kynurenic acid (A and C) or Locke's solution (B and D) was injected into the contralateral DNLL (A and B) or the contralateral IC (C and D). F0 amplitude under Condition C before injection served as the baseline condition (F0 amplitude = 1) for normalization. See Fig. 3 for abbreviations. Note that F0 amplitudes were significantly enhanced across conditions after blocking of glutamate receptors in the contralateral DNLL (A, $P = 0.023$), and generally reduced after blocking of glutamate receptors in the contralateral IC (C, $P = 0.001$), which are revealed by repeated-measures ANOVAs.

are generally in agreement with the notion that introducing a difference between signal and masker in binaural configurations improves auditory representations of the signal, as shown by previous reports on binaural unmasking/spatial unmasking of auditory responses in the IC in laboratory animals (e.g. Caird *et al.*, 1991; Mandava *et al.*, 1996; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Ratnam & Feng, 1998; Palmer *et al.*, 2000; Lin & Feng, 2003; Lane & Delgutte, 2005) and previous reports on binaural unmasking of brainstem FFRs in humans (Wilson & Krishnan, 2005).

It would be of interest to know whether the binaural unmasking of FFRs recorded in the rat IC shares similar mechanisms with the binaural masking level difference (BMLD) as measured in the IC of other species. The BMLD is a well-studied psychophysical phenomenon showing that the signal, presented at both ears and masked by a noise masker presented at both ears, becomes more easily detected when either the interaural phase of the signal or that of the masker is reversed (Hirsh, 1948). Thus, the BMLD measures the ability of listeners to use a difference between signal and masker in binaural attributes to improve their detection of the signal against the masking noise. The BMLD has been demonstrated on single neurons in both the guinea-pig IC (e.g. Caird *et al.*, 1991; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Palmer *et al.*, 1999, 2000; Palmer & Shackleton, 2002) and the chinchilla IC (Mandava *et al.*, 1996). In general, the BMLD is considered to be a low-frequency phenomenon, because it has been found to be efficient when the frequency of the signal is below 1–2 kHz (e.g. Hirsh, 1948; Caird *et al.*, 1991; Mandava *et al.*, 1996). Either reducing the interaural correlation of the masking noise or introducing a signal (e.g. 500-Hz tone) to the fully correlated masking noise is able to weaken the quasiperiodic noise delay functions (NDFs), which are modulations of neural responses to interaurally correlated noise with

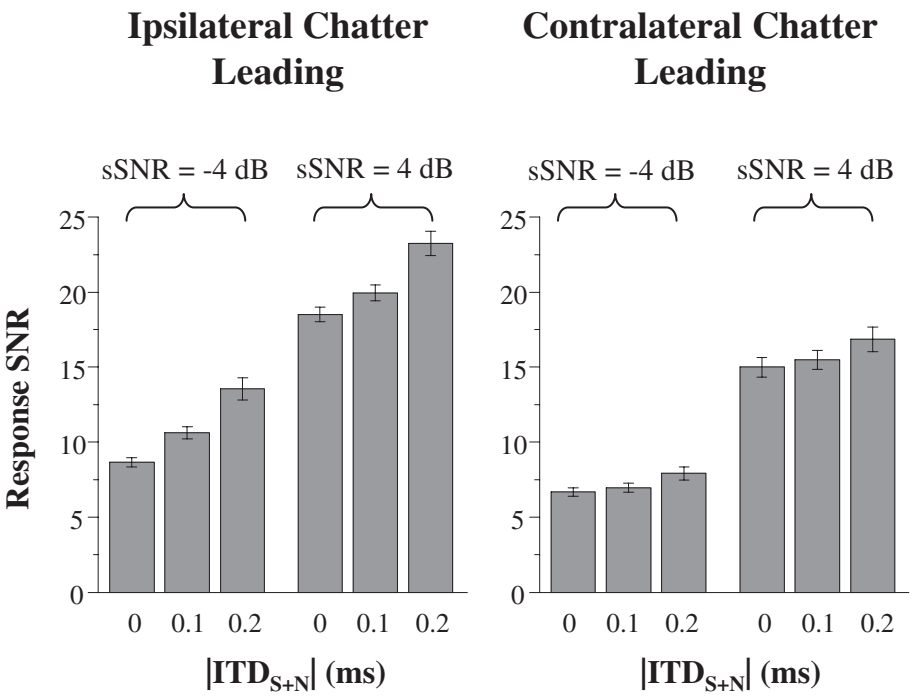

FIG. 5. Relative response signal-to-noise ratios (rSNRs) of IC FFRs when the chatter was co-presented with white noise with different ITD disparities ($|ITD_{S+N}|$) before injection manipulations. rSNRs were presented separately for conditions when ipsilateral chatter led contralateral chatter (left) and conditions when contralateral chatter led ipsilateral chatter (right). Numbers associated with each bar represent the $|ITD_{S+N}|$ value in milliseconds. sSNR, stimulus signal-to-noise ratio.

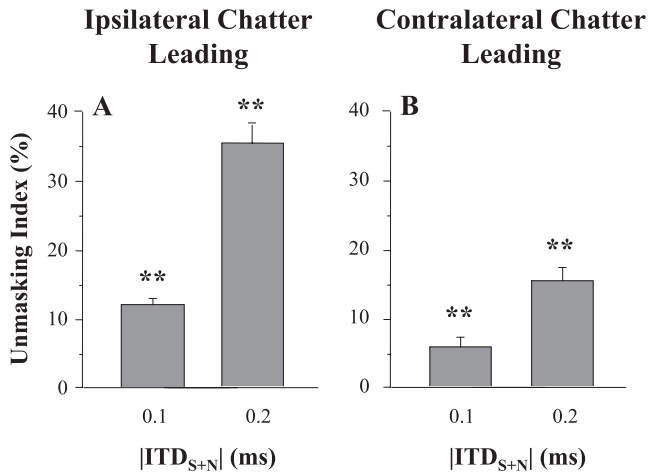

FIG. 6. Unmasking indices (UIs) of IC FFRs when the chatter was co-presented with white noise with different ITD disparities ($|ITD_{S+N}|$) before injection manipulations. UIs were presented separately for conditions when ipsilateral chatter led contralateral chatter (A) and conditions when contralateral chatter led ipsilateral chatter (B). Numbers associated with each bar represent the $|ITD_{S+N}|$ value. Note that introducing either 0.1- or 0.2-ms ITD disparity elicited a significant binaural unmasking effect regardless of the chatter-ITD (**$P < 0.01$, repeated-measures ANOVA).

changing interaural delay. Palmer *et al.* have suggested that the BMLD, which is based on the processing of cross-correlation of the signals at the two ears and the contributions of different populations of neurons under different binaural configurations, can be explained by the decorrelation of the responses to interaurally correlated noise when the tone signal is presented (Palmer *et al.*, 1999; Palmer & Shackleton, 2002). In the present study, the F0 of the signal (the chatter) was above 2 kHz, suggesting that measurements of binaural unmasking based on synchronized FFRs of a population of neurons exhibit several features that have not been revealed in measurement of BMLD based on single-unit firing counting. By contrast, as FFRs to binaural stimulation are ITD-dependent, different populations of IC neurons contribute to FFRs differently under different binaural configurations. In other words, when the signal-ITD is different from the masker-ITD, some IC neurons are driven only by the signal but not by the noise masker, leading to an improvement in the SNR of FFRs. This population-disparity strategy for unmasking FFRs may be similar to that for BMLD. Moreover, the results of the present study indicate that when the signal at the ipsilateral ear leads that at the contralateral ear, both the contralateral DNLL and the contralateral IC contribute to the unmasking of FFRs, showing additional important mechanisms underlying the unmasking of FFRs. However, it is not clear whether the contralateral DNLL and/or contralateral IC contribute to BMLDs measured in the IC.

As mentioned above, the BMLD has been demonstrated in single neurons in both the guinea-pig IC (e.g. Caird *et al.*, 1991; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Palmer *et al.*, 1999, 2000; Palmer & Shackleton, 2002) and the chinchilla IC (Mandava *et al.*, 1996). However, considering that Lane & Delgutte (2005) have reported that signal–masker spatial separation improves only the population thresholds but not necessarily the single-unit thresholds of IC responses to the noise-masked signal in cats, analyses of FFRs (based on synchronized activities of a population of neurons) in various species are more advantageous than counting numbers of single-unit action potentials in estimating binaural unmasking of IC responses. In particular, investigation of binaural unmasking of IC FFRs in laboratory animals helps to explain the reports that human brainstem FFRs are resistant to noise masking (Russo *et al.*, 2004) and can be unmasked by binaural processing (Wilson & Krishnan, 2005).

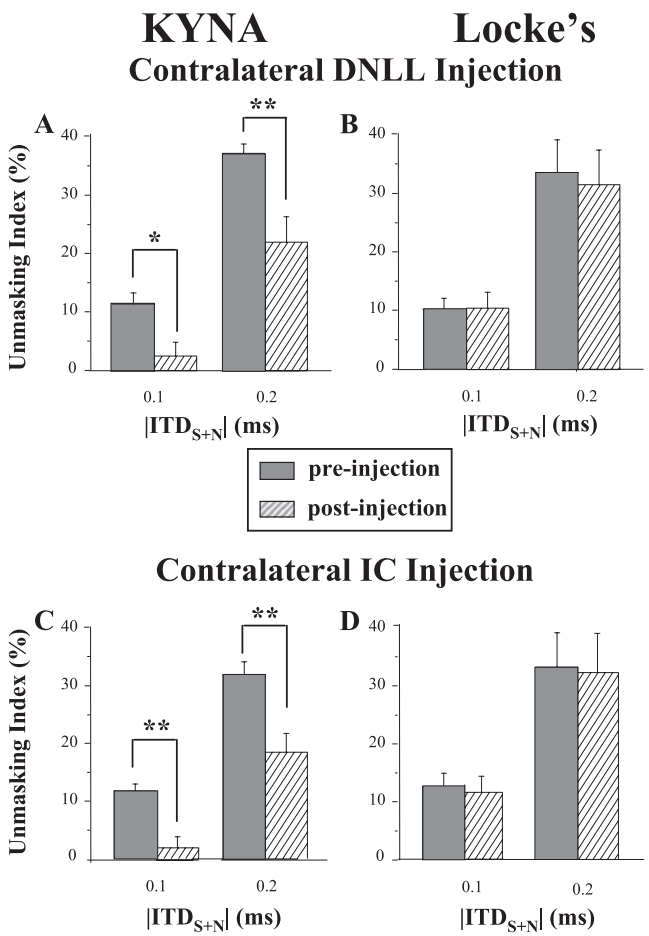

FIG. 7. Effects of blocking of the contralateral DNLL or the contralateral IC on binaural unmasking of FFRs when ipsilateral chatter led contralateral chatter. Unmasking indices (UIs) of FFRs under different ITD disparities are showed before (shaded bars) and after (hatched bars) injection of either kynurenic acid (A and C) or Locke's solution (B and D) into the contralateral DNLL (A and B) or the contralateral IC (C and D). See Fig. 5 for explanation of symbols and abbreviations. Note that blockade of glutamate receptors in either structure significantly reduced UIs under either 0.1- or 0.2-ms ITD disparity between chatter and noise. *$P < 0.05$, **$P < 0.01$, paired-samples *t*-tests.

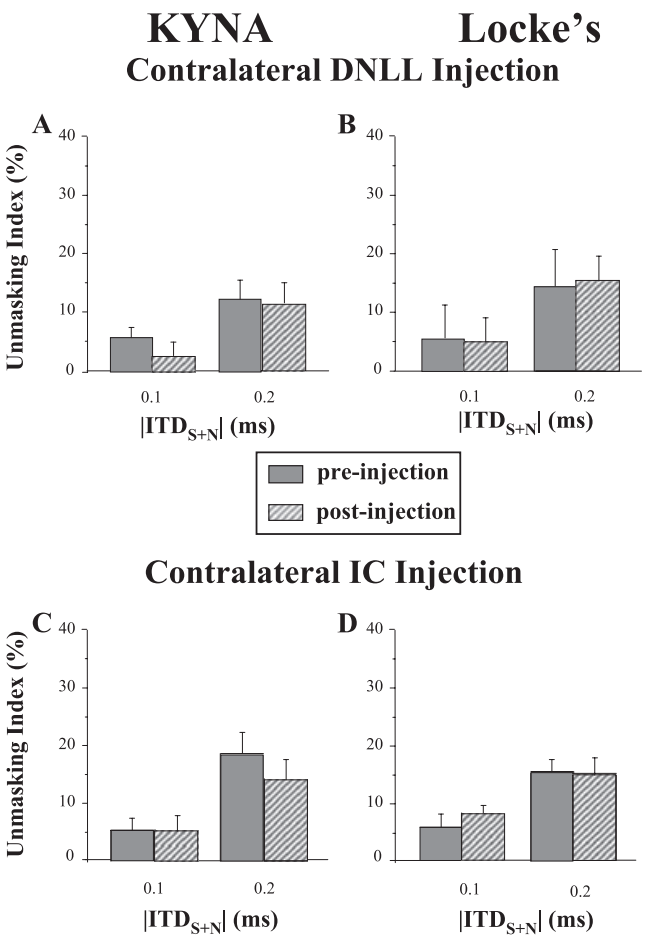

FIG. 8. Effects of blocking the contralateral DNLL or the contralateral IC on binaural unmasking of FFRs when contralateral chatter led ipsilateral chatter. UIs of FFRs under different ITD disparities are shown before (shaded bars) and after (hatched bars) injection of either kynurenic acid (A and C) or Locke's solution (B and D) into the contralateral DNLL (A and B) or the contralateral IC (C and D). See Fig. 5 for explanation of symbols and abbreviations. Note that blockade of glutamate receptors in either structure did not significantly change UIs under either 0.1- or 0.2-ms ITD disparity between chatter and noise.

Binaural unmasking of IC FFRs may be associated with neural correlates of the precedence effect (Yin, 1994; Litovsky *et al.*, 1999), which induces perceptual fusion of correlated sounds in both humans (Litovsky & Shinn-Cunningham, 2001; Li *et al.*, 2005) and rats (Kelly, 1974; Hoeffding & Harrison, 1979). The precedence-effect-induced perceived spatial separation between signal and masker improves processing of target signals in humans (e.g. Freyman *et al.*, 1999; Li *et al.*, 2004; Wu *et al.*, 2005; Huang *et al.*, 2008). The results of binaural unmasking of IC FFRs reported here suggest that the precise processing of signal details in the rat IC can be refined by binaural/spatial processing, which may contribute to solving the auditory 'what' and 'where' difficulties in noisy, reverberant environments.

Contralateral DNLL and IC contribute to binaural unmasking of IC FFRs

If EE neurons play the major role in inducing binaural IC FFRs, they may be affected by input from both the contralateral DNLL and the contralateral IC, because EE neurons in the recorded IC and most neurons in both the contralateral IC and the contralateral DNLL are activated by stimulation at the ear ipsilateral to the recorded IC.

For inputs from the contralateral IC, although the existence of a GABAergic projection through the commissure of IC has been described (González-Hernández *et al.*, 1996; Hernández *et al.*, 2006), a non-GABAergic (Zhang *et al.*, 1998) and a strong glutamatergic projection (Saint Marie, 1996) has also been confirmed. In particular, Malmierca *et al.* (2005) have reported that auditory responses in the rat IC to either monaural or binaural stimulation are affected by commissural blockade. The results of the present study confirm that the intercollicular connection makes a contribution to the formation of IC FFRs in rats. It is suggested that ipsilateral stimulation drives not only EE neurons in the recorded IC but also EE, EI and EO neurons in the contralateral IC, which, in turn, further activate EE neurons in the recorded IC. In other words, input from the contralateral IC is one of the sources leading to IC FFRs driven by ipsilateral stimulation. The reduction of binaural unmasking of IC FFRs following blocking of the contralateral IC is due to the reduction of the signal-to-masker ratio in the neural representation of stimuli. It is important to know whether the intercollicular connection also contributes to human brainstem FFRs.

By contrast, IC neurons receive inhibitory (GABAergic) influence from the contralateral DNLL (Burger & Pollak, 2001; Faingold *et al.*, 1993; Kelly & Li, 1997; Kidd & Kelly, 1996; Li & Kelly, 1992; Van Adel *et al.*, 1999; Zhang *et al.*, 1998; for a review see Li & Yue, 2002). Clearly, ipsilateral stimulation drives EE neurons in the (recorded) IC, all types of neurons in the contralateral IC, as well as neurons in the contralateral DNLL. Both the present study and our previous study (Ping *et al.*, 2008) confirm that the contralateral DNLL plays a role in suppressing IC FFRs in quiet because IC FFRs were enhanced by blocking of the contralateral DNLL when no masker was presented. Interestingly, in the present study when the masker was presented and the ipsilateral chatter led the contralateral chatter, binaural unmasking was reduced significantly by blocking of excitatory glutamate transmissions in the contralateral DNLL, suggesting that GABAergic projections from the contralateral DNLL play a role in forming binaural unmasking in the IC. It is well known that inhibitory inputs to the IC shape binaural responses of IC neurons (Li & Kelly, 1992; Ito *et al.*, 1996; Kidd & Kelly, 1996; Kelly & Li, 1997; Van Adel *et al.*, 1999; Burger & Pollak, 2001). In addition, Lin & Feng (2003) have reported that iontophoretic application of bicuculline, a $GABA_A$ receptor antagonist, into the frog IC markedly degraded binaural processing involved in spatial unmasking of the IC. Thus, the results of the present study suggest that ipsilateral stimulation (relative to the recorded IC) drives the contralateral DNLL, which not only inhibits IC FFRs but also facilitates binaural unmasking of FFRs in the IC. The unmasking effect may be caused by the function of the DNLL in both facilitation of binaural responses to the signal and suppression of responses to the noise masker. Klug *et al.* (2002) and Xie *et al.* (2005) have shown that in the free-tailed bat IC, neural selectivity to species-specific calls is primarily attributed to local GABAergic inhibition. Thus, in the present study, the interruption of GABAergic innervations from the contralateral DNLL might also disrupt the response selectivity of IC neurons to the tail-pain chatter, leading to a reduction of FFRs to the chatter against noise masking.

As both enhancement of signal inputs and suppression of masker inputs can improve the signal-to-masker ratio in neural representation of acoustic stimuli, the functional integration of excitatory inputs from the contralateral IC and inhibitory inputs from the contralateral DNLL is a critical issue for future studies of binaural unmasking of FFRs. As mentioned in the introduction, scalp-recorded FFRs in humans can be used to study the neural coding of critical features of speech sounds (Hall, 1979; Krishnan, 2002; Krishnan *et al.*, 2004; Russo *et al.*, 2004), top-down regulation of brainstem auditory responses (Galbraith *et al.*, 2003) and language-experience-related neural plasticity (Galbraith *et al.*, 2004; Krishnan *et al.*, 2005; Xu *et al.*, 2006; Swaminathan *et al.*, 2008). The resistance of human brainstem FFRs to noise masking (Russo *et al.*, 2004) and binaural unmasking of FFRs (Wilson & Krishnan, 2005) may be also useful for studying mechanisms underlying the 'cocktail party problem' as proposed by Cherry (1953). Thus, investigation of mechanisms underlying binaural unmasking of IC FFRs (the present study) and higher-level structure FFRs (Du *et al.*, 2009) to species-specific calls in rats is important for building animal models in this line of research.

Acknowledgements

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Abbreviations

BMLD, binaural masking level difference; C, contralateral; C/I, contralateral chatter leading; DNLL, dorsal nucleus of the lateral lemniscus; FFR, frequency-following response; FFT, fast Fourier transform; I, ipsilateral; I/C, ipsilateral chatter leading; IC, inferior colliculus; ISI, inter-stimulus interval; KYNA, kynurenic acid; NDF, noise delay function; rSNR, response signal-to-noise ratio; SNR, signal-to-noise ratio; sSNR, stimulus signal-to-noise ratio; UI, unmasking index.

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