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RESEARCH ARTICLE

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The commissure of the inferior colliculus shapes frequency response areas in rat: an in vivo study using reversible blockade with microinjection of kynurenic acid

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Abstract The commissure of the inferior colliculus (CoIC) interconnects corresponding frequency-band laminae in the two inferior colliculi (ICs). Although the CoIC has been studied neurophysiologically in vitro, the effect of the CoIC on the responses of IC neurons to physiological stimuli has not been addressed. In this study, we injected the glutamate receptor blocker kynurenic acid into one IC while recording the frequency response areas (FRAs) of neurons in the other, to test the hypothesis that frequency response properties of IC neurons are influenced by commissural inputs from the contralateral IC. Following blockade of the commissure, 10 of 12 neurons tested exhibited an increase or a decrease in their FRAs. In most neurons (9/12) the response area changed in the same direction, irrespective of whether the neuron was stimulated monaurally (at the ear contralateral to the recorded IC) or binaurally. In one neuron, blockade of the CoIC resulted in an expansion of the response area under binaural stimulation and a contraction under monaural stimulation. In the remaining two units, no effect was observed. Changes in response areas that exceeded the criterion ranged between 17 and 80% of control values with monaural stimulation, and 35 and 77% with binaural stimulation. Area changes could also be accompanied by changes in spike rate and monotonicity. From our observation that FRAs contract following commissure block, we infer that the commissure contains excitatory fibres. The expansion of response areas in other cases, however, suggests that the commissure also contains inhibitory fibres, or that its effects are mediated by disynaptic as well as monosynaptic circuits. The small sample size precludes a definitive conclusion as to which effect predominates. We conclude that inputs from the contralateral IC projecting via the CoIC influence the spectral selectivity and response gain of neurons in the IC.

Keywords Auditory pathway · Single unit · Frequency response area · Glutamate receptors

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Introduction

The inferior colliculi (ICs), paired structures in the midbrain, are interconnected by a bundle of fibres called the commissure of the inferior colliculus (CoIC; Coleman and Clerici 1987; Saldaña and Merchán 1992; Malmierca et al. 1995). This commissure provides the final opportunity for interactions between the two sides of the auditory pathway prior to the auditory cortex, apart from a small component from the inferior colliculus to the contralateral medial geniculate body (Chernock and Winer 2001; Malmierca and Merchán 2003).

In a previous study we have demonstrated that commissural projections interconnect mirror symmetric regions of the ICs representing similar frequency bands (Malmierca et al. 1995), and thus contribute to the laminar pattern displayed by other ascending afferents terminating in the IC (Malmierca et al. 1999; Malmierca and Merchán 2003).

Many neurons in the IC, including some projecting to the thalamus, send projections into the commissure (Oliver et al. 1991; Malmierca et al. 1995). The weight of these projections suggests that the commissure makes an important contribution to the processing of sound in the auditory pathway, yet little is known about its function. No deficits in an animals ability to localize sounds were found in a behavioural study in the ferret where the IC was ablated (Kelly and Kavanagh 1994) but other aspects of auditory processing, such as frequency analysis and temporal resolution, have not been tested. Anatomical studies suggest that the commissural projection might be

Table 1 Number of units used in each stimulus and experimental condition (*FRA* frequency response areas,*KA* kynurenic acid)

Stimulus condition	Classification of FRA type	Analysis of control FRA	Injection of Lockes solution	Injection of KA
Monaural contralateral	79	12	5	12
Binaural	46	8	4	12
Monaural ipsilateral	10	–	–	–
Total units in group	79	12	5	12

glutamatergic (Saint Marie 1996; Zhang et al. 1998), but physiological recordings of IC neurons in vitro show that stimulation of CoIC fibres elicits both inhibitory and excitatory postsynaptic potentials (IPSPs and EPSPs, respectively) (Smith 1992; Moore et al. 1998). To date, however, the functional role of the commissural connection has not been studied neurophysiologically in vivo.

The processing of sounds depends on the analysis of their frequency content by the cochlea and the central nervous system. A recent microiontophoretic study in the guinea-pig demonstrated that both γ-aminobutyric acid (GABA) and glycine shapes the frequency response areas of IC neurons (LeBeau et al. 2001). However, the origins of the inputs shaping frequency response areas in the IC have not been investigated. In the present study, we measured the frequency response areas of neurons in one IC while pharmacologically blocking activity in its contralateral counterpart to test the hypothesis that the CoIC influences frequency processing in the IC. Preliminary descriptions of the present data have been reported elsewhere (Malmierca et al. 2001, 2002a).

Materials and methods

The methods for surgical preparation, animal maintenance, single-unit recording, and auditory stimulation were similar to those described previously (LeBeau et al. 1996, 2001; Rees et al. 1997). In this account only essential details of methods are given.

Experiments were performed on adult pigmented rats (*Rattus norvergicus*, Rj: Long Evans) of either sex weighing between 180 and 420 g (n=38). All experiments were carried out with the approval of, and using methods conforming to, the standards of the University of Salamanca Animal Care Committee. Animals were anaesthetised with urethane (1.5 g/kg i.p., 20% solution). Supplementary doses of urethane (0.5 g/kg i.p.) were given as required. The animals body temperature was maintained at 38°C. The animal was placed in a stereotaxic frame in which the ear bars were replaced by hollow speculi that accommodated a sound delivery system. Craniotomies were performed to expose the cortical surface over the inferior colliculi on both sides. The animal was placed inside a sound attenuating booth and stimuli (noise and pure tones) were produced by a waveform generator (Hewlett Packard-8904A Multifunction Synthesizer) and delivered through a closed acoustic system consisting of two Sony MDR-E868 earphones. Tone and noise bursts could be independently attenuated at the output to the transducers by digital attenuators.

Recording of neuronal activity and delivery of kynurenic acid

A custom-made electrode holder attached to a microdrive (model 6000, Burleigh, Fishers, NY, USA) was used to place a tungsten recording electrode into one IC simultaneously with a micropipette filled with kynurenic acid (KA) into the other. Neuron location in the IC was estimated using physiological criteria of tonotopicity and response reliability as well as histological verification. Extracellularly recorded action potentials were amplified (×10,000), filtered (0.3–3 kHz), discriminated and time-stamped with an accuracy of 10 μs by a CED-1401plus Laboratory Interface (Cambridge Electronic Design, Cambridge, UK). Kynurenic acid in Lockes solution (0.4 mg/ml) was introduced into the contralateral IC by pressure injection through a glass micropipette (1.0 mm OD, 0.75 mm ID, tip diameter 20–40 μm). The pipette was back filled and connected to a 10 ml syringe by flexible tubing. The volume injected was determined by monitoring the position of the meniscus in the pipette. The flow was stopped by releasing the pressure through a three-way tap. A silver wire sealed into the tubing allowed the pipette to be connected to an amplifier through which neural activity could be recorded in order to determine the best frequency of the injection site (Li and Kelly 1992). In all cases the best frequency (BF) at the site of injection never differed by more than 2 kHz from the BF of the unit recorded in the other IC. The IC was temporarily inactivated by injection of 1–2 μl KA. As a control in some experiments, Lockes solution alone was injected using the same technique as for KA (Table 1).

Generation of frequency response area maps

Frequency response areas (FRAs) for single neurons recorded with the tungsten electrode were obtained to either monaural or binaural stimuli. Binaural stimuli were presented at the same level to both ears and with zero interaural time delay. The method employed to construct FRAs was similar to that described by Evans (1979). A pseudorandom sequence of tone-bursts (50 ms duration, repetition rate 5/s, 5 ms rise/fall time), varying in frequency by 51 logarithmically spaced steps and in level by 5 dB steps over a 90-dB range, was presented to the animal. The number of spikes fired in response to each tone was plotted as a bar positioned at the frequency and intensity coordinates of the stimulus eliciting the response. Bar length was proportional to the number of spikes counted for each stimulus presentation (Fig. 1).

Data analysis

We measured the area of a units FRA under control and experimental conditions using the method described by LeBeau et al. (2001). To calculate the total area we counted the number of driven response values in each intensity row of the response area, and summed the values of all the intensity rows to obtain the total area (see LeBeau et al. 2001 for full details). This gave a measure in arbitrary units derived from the number of stimuli that activated the neuron. After application of KA or Lockes solution, recordings were continued until the neuron had recovered or until the unit was lost, whichever occurred sooner. Changes in the size of response areas following application of KA were normalized with respect to the control and plotted as a function of time.

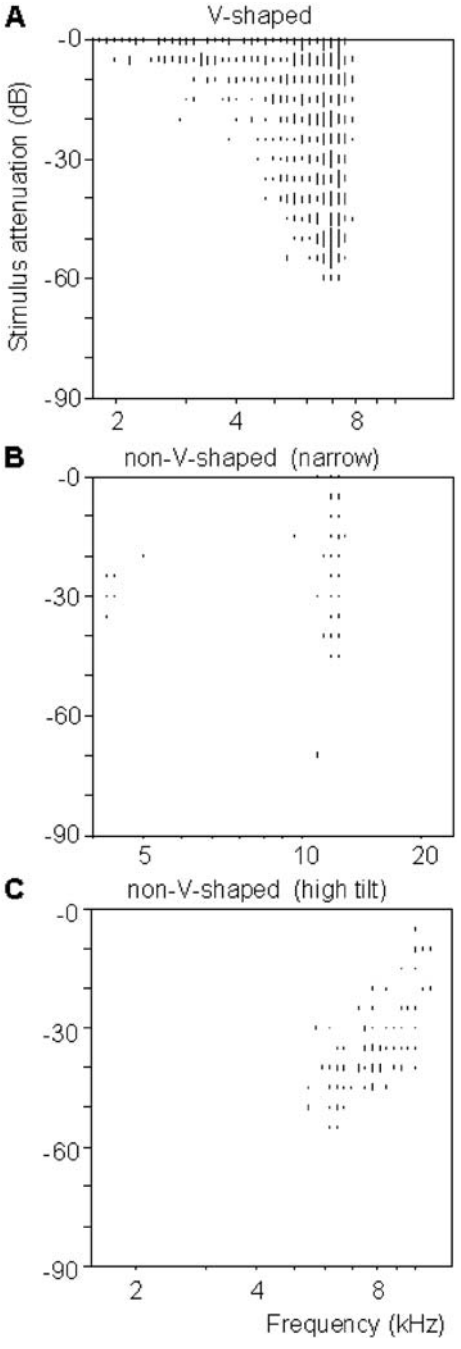

Fig. 1A–C Examples of frequency response areas (FRAs) recorded from the inferior colliculus of rat. The number of spikes fired in response to stimulus is plotted as a bar positioned at the frequency and intensity coordinates of the stimulus eliciting the response. Bar length is proportional to the number of spikes counted for each stimulus presentation. **A** V-shaped FRA, and **B,C** non-V-shaped (narrow and high-tilt, respectively) FRAs

Histological verification of recording sites

At the end of each experiment the animal was given a lethal dose of sodium pentobarbitone (Nembutal) and then perfused. The brain was processed histologically to recover the tracks of both electrodes and the electrolytic lesions made with the tungsten recording electrode (see LeBeau et al. 2001 for details). All units were localized to the IC. Most units used to define the FRA types were in the central nucleus, as defined in the rat by Malmierca et al. (1993), but it was not always possible to identify the location of units recorded in the KA-block experiments to a particular subdivision.

Results

Seventy-nine neurons (BF range 1–34 kHz) from 38 rats were recorded from the IC in response to monaural and/or binaural stimulation. The responses of all these neurons were used to classify FRAs in rat IC according to their shape (Fig. 1), and 29 neurons from this total were used in the remaining procedures (Table 1). For 12 neurons, FRAs were recorded repeatedly over a period of up to 84 min to determine the variability of the FRAs over time in the absence of any injection into the IC (Fig. 2A,B). Seventeen neurons were recorded before, during and after the pressure injection of Lockes solution (n=5) or KA (n=12) into the contralateral IC (Figs. 3 and 4). The numbers of units, grouped according to stimulus condition and experimental procedure, are summarized in Table 1.

FRA types in rat

Based on the pattern of the FRA (e.g. Fig. 1), we could classify FRAs in rat into one of six types according to the scheme of LeBeau et al. (2001) for IC neurons in guinea-pig. These types can be grouped into two broad classes: V-shaped (n=45 with contralateral monaural stimulation, n=3 with ipsilateral monaural stimulation, and n=41 with binaural stimulation) and non-V-shaped (n=34 with contralateral monaural stimulation, n=7 with ipsilateral monaural stimulation, and n=29 with binaural stimulation).

V-shaped FRAs (Fig. 1A) are characterized by a narrow tip at the neurons BF, which broadens progressively on either side of BF as sound level is increased. Neurons in which stimulus-evoked firing showed no reduction at the highest stimulus levels are termed monotonic V-shaped (Fig. 1), whereas those in which there was a marked reduction in discharge rate at high stimulus levels, evident from the shorter bar lengths, are termed non-monotonic-V-shaped.

Non-V-shaped FRAs (Figs. 1B,C) consist of other types that do not conform with the V-shaped types describe above. FRAs in this group are more heterogeneous with respect to shape and can be assigned to one of the following subtypes: narrow (Fig. 1B), closed, low- or high-tilt (Fig. 1C), and double-peaked.

For most neurons in the sample (n=59), the FRA type was the same irrespective of whether the stimuli were presented monaurally or binaurally, but in a minority (n=6) monaural and binaural stimulation elicited different FRA types.

Effect of blocking the commissure of the IC on frequency response areas

Because of the need to hold units for long periods to follow the time-course of the KA effect and its recovery, it was not feasible to make more than one control measurement prior to injecting KA. Therefore, to obtain an estimate of the variance of the FRA measurements and to validate a criterion for the changes in FRA size, we made repeated control measures of FRAs in 12 control neurons for up to 84 min to mimic the time-course of measurements made in experimental cases. For each unit, and separately for each stimulus condition (monaural or binaural), we calculated the mean area of the FRAs, and for each FRA, the ratio of its area relative to the mean was determined. This ratio, which is greater than unity for areas greater than the mean and less than unity for areas smaller than the mean, is referred to as the *area change ratio* (Fig. 2). The ratios for all units in the control sample were pooled to obtain the mean (by definition equal to 1) and the standard deviation (SD) of the ratios for the control group according to stimulus type. The interval defined by the mean ±3SD was used as the boundary for a significant change in the experimental data. The actual limits of this interval (*horizontal dashed lines* in Fig. 2) were different for monaural (1±0.16, Fig. 2A) and binaural stimulation (1±0.27, Fig. 2B), representing 16% and 27% changes in area ratio, respectively. For the experimental condition, the FRA taken prior to the injection was used as a control and provided the reference value for calculating the area change ratios for the remaining FRAs in the series. Only units where ratios exceeded the criterion defined above were accepted as demonstrating an effect of commissural blockade (e.g. Fig. 3).

For five units we analysed the effect of injecting Lockes solution alone into the IC contralateral to the recording site as a control for the effects of pressure injection (Table 1; Fig. 2C,D). The variation in the area of the FRAs following these injections are confined within the ±3SD boundaries chosen as the criterion for a significant change in area. These findings demonstrate that our results with KA injections reflect a genuine effect of glutamate receptor blockade and are not artefacts arising from the injection or another uncontrolled condition.

Our main finding is that most neurons (83%, 10/12) recorded in the IC after blocking its contralateral counterpart with KA show a significant change in the area of their FRAs. Area changes in FRAs following KA injection were generally (9 of 10 neurons) in the same direction (expansion or contraction), irrespective of whether the stimuli were presented monaurally or binaurally. However, in one case the direction of the effect depended on the pattern of stimulation (Fig. 4D). In this case, under monaural stimulation commissure block lead to a contraction in the FRA, whereas with binaural stimulation the FRA expanded. The effect of KA could take up to 20–30 min after its injection to reach maximal, and the effect lasted for a further 40–60 min. In all cases but one, evidence for partial or complete recovery was observed over the following hour (Fig. 3 and Fig. 4A,B).

Of the tested neurons, 50% showed a decrease (Fig. 4C) in the area of their FRAs with monaural stimulation (n=6, mean ±SD 35±13%, range 17–56%; e.g. Fig. 3A1–A3 and Fig. 4D), whereas 36% showed a decrease with binaural stimulation (n=4, mean ±SD 51±10%, range 35–61%; Fig. 3B1–B3 and Fig. 4D). (Two units in this group showed no significant change with binaural stimulation, Fig. 4D). Twenty-five percent (n=3) of the sample showed a significant expansion (Fig. 4C) of their FRAs with either monaural (n=2, mean ±SD 54.5±25.5, range 29–80%; Fig. 4D), and/or binaural stimulation (n=2, mean ±SD 76 ±1, range 75–77%; Fig. 3D1–D3 and Fig. 4D); the FRA of

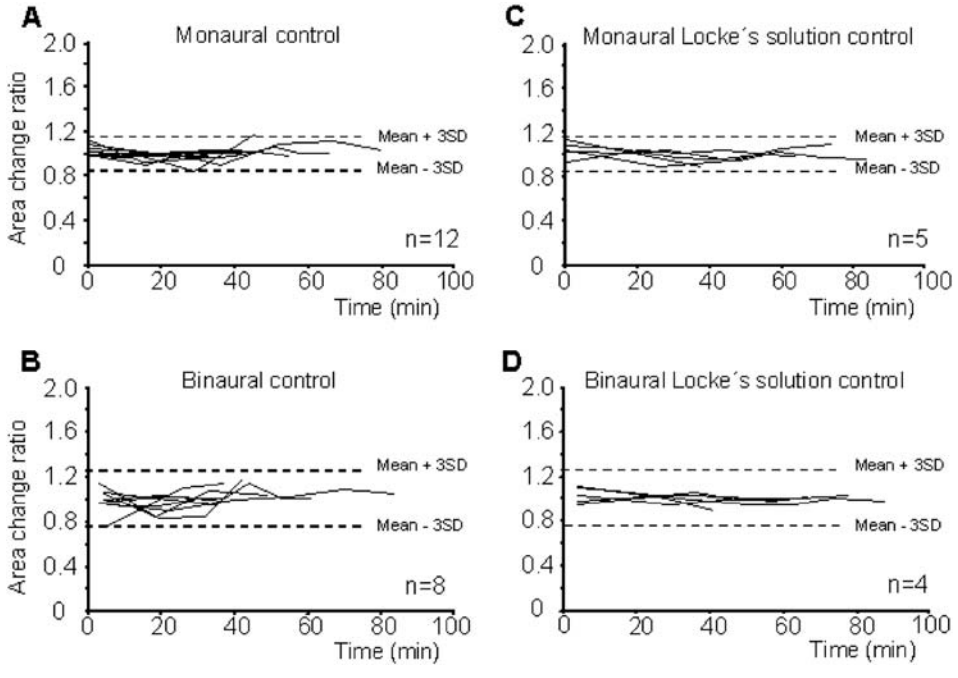

Fig. 2A–D Change in frequency response area (FRA) as a function of time under control conditions expressed relative to mean area for each unit (area change ratio; see Materials and Methods section for details). **A** Monaural and **B** binaural stimulation. *Horizontal dashed lines*, representing mean ±3SD of the area change ratio, provide the criteria for a significant experimental effect. **C,D** Equivalent plots where an injection of Lockes solution (control vehicle) into the IC contralateral to the recording was made after the first FRA measurement in each series

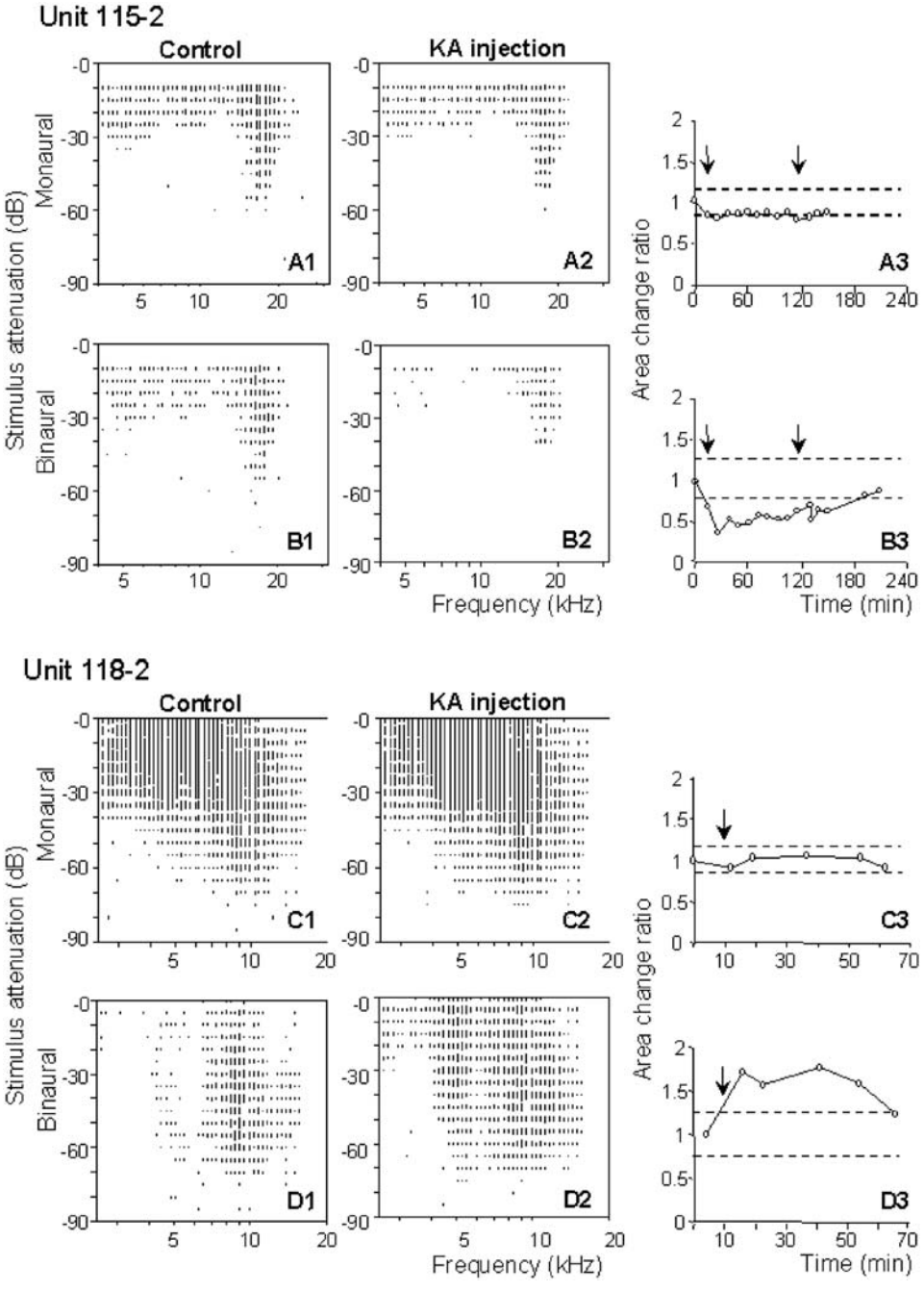

Fig. 3A–D Examples of two units with frequency response areas (FRAs) that decreased (**A1–A3** monaural, **B1–B3** binaural), and increased (**C1–C3** monaural, **D1–D3** binaural) after reversible block of the commissure of the inferior colliculus with kynurenic acid (KA) under some stimulus conditions. **A1–A3** is the smallest significant change in the whole sample. Panels **A3, B3, C3** and **D3** show the area of the FRA relative to the first control area following one or two injections of KA, at times indicated by the arrows. *Horizontal dashed lines* represent the mean ±3SD of the area change ratio for the controls (see Fig. 2)

one unit in this group expanded with both stimulus types. An example of the change seen in one of these units (Fig. 3D1) shows an island of weak response on the low-frequency side of the binaural FRA that responds more robustly and expands to become contiguous with the main region of the FRA following commissural blockade (Fig. 3D2). One unit in the sample showed a mixed effect; namely, there was a contraction of the FRA with monaural stimulation (39%, Fig. 4D) whereas binaural stimulation was associated with an expansion of 68% (Fig. 4C). The remaining 17% (n=2) of the units in the sample did not show a significant effect with either monaural or binaural stimulation (Fig. 4C). Plots depicting the area changes for all the units in the sample (Fig. 4A,B) suggest that the largest changes are measured under binaural stimulation, but the sample size is insufficient to be conclusive.

In addition to the changes in the area of the FRA following blockade with KA, in some units changes in the firing rate were also apparent. These can be seen by comparing the length of the response bars for equivalent stimuli in Fig. 3 before (control) and after KA injection. These changes were quantified by counting the spikes fired at each stimulus level along selected isofrequency lines in the FRAs to obtain rate-level functions. For unit 115–2 (Fig. 3A,B), the peak in the rate-level function at BF declined from 8 to 5 spikes/stimulus with monaural stimulation and from 9 to 3 spikes/stimulus with a binaural

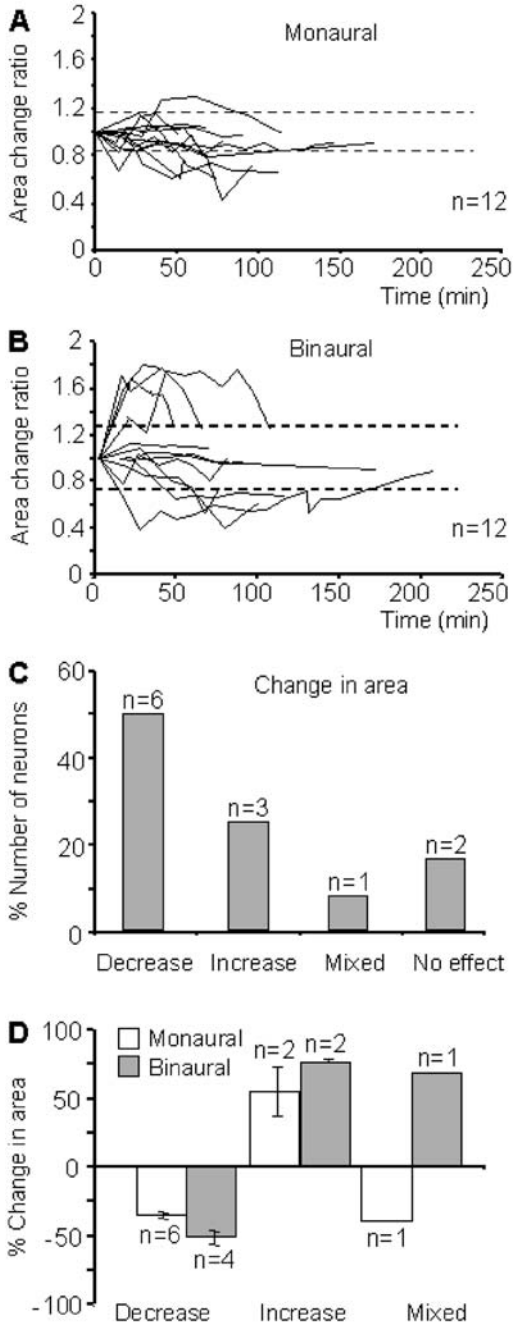

Fig. 4A–D Area changes for all units in the sample following injection of kynurenic acid (KA) under conditions of **A** monaural stimulation and **B** binaural stimulation. **C** Percentage of neurons showing expansion or contraction (greater than criterion; see Results section) of their frequency response areas (FRAs) following reversible block of the commissure of the inferior colliculus with kynurenic acid (KA). The values on the histogram bars are the number of units in which the area decreased under at least one of the monaural or binaural stimulus conditions (*Decrease*), increased with either monaural and/or binaural stimulation (*Increase*), decreased with monaural but increased with binaural stimulation (*Mixed*), or showed *No effect* with either monaural or binaural stimulation. **D** Mean percentage change (error bars represent one SEM) in area of FRAs with monaural or binaural stimulation following block of commissure

stimulus. Consistent changes were also apparent at other frequencies. For unit 118–2 with binaural stimulation (Fig. 3D), the maximum firing rate as a function of level did not change with KA injection but the rate-level function changed shape from non-monotonic to monotonic. With monaural stimulation neither the firing rate nor the shape of the rate-level function changed with KA injection.

Discussion

By using KA injections to inactivate neurons in one IC that project through the commissure to the contralateral side, we have demonstrated that commissural projections influence the frequency response properties of neurons in the IC of rat. To the best of our knowledge this is the first study to analyse the functional role of the CoIC in vivo. Response areas showed expansion or contraction and for most units the change was in the same direction under both monaural and binaural stimulation. Changes in the area of FRAs could be accompanied by changes in firing rate and the degree of monotonicity, suggesting that commissural fibres can influence the response gain of neurons in the IC. Although a detailed analysis of the FRA types is not within the scope of the present report, we have also shown that the FRA types in IC of rat are qualitatively similar to those described in guinea-pig (LeBeau et al. 2001). Before discussing the functional significance of our results, some comments on the methodology are appropriate.

We measured changes in area and applied two different levels of significance for monaural (16%) and binaural (27%) stimulation (Fig. 2). These values are similar to the criterion of 20% for significant changes in firing rate that was applied in previous studies using KA injection to block input from the dorsal nucleus of the lateral lemniscus to the IC (Li and Kelly 1992; Burger and Pollak 2001).

Our study is based on single units and is limited by the small sample of units with inactivation of the commissural projection that were studied owing to several technical difficulties. These include ensuring that the BFs of the sites recorded with the injection and recording electrodes were similar, and maintaining recording contact with a neuron while the pressure injection was made. The marked difference in the time-course of the KA block in different units might be explained by several factors including the distance of the pipette (and therefore the diffusion time of the KA) from the commissurally projecting neurons that influenced the recorded neuron (e.g. Foeller et al. 2001; Kelly and Zhang 2002). Commissural fibres project from one IC to the other with a laminar organization, which reflects the tonotopic organisation of the IC (Malmierca et al. 1995). Although we attempted to place the electrodes in corresponding frequency-band laminae by ensuring the BFs of the injection and recording sites were always within 2 kHz of one another, we had no control over the position of the electrodes within a lamina. Thus, even when a frequency match was achieved there might be

considerable variation in the distance of the pipette tip from the projecting neurons, and therefore in the efficacy of the blockade.

The examples shown in Fig. 3 and the sample data in Fig. 4 suggest that changes in the size of FRAs with blockade of the CoIC are more dramatic with binaural stimulation than with monaural. This finding is consistent with the known organization of the ascending pathways to the ICs. Monaural stimulation of the ear contralateral to the recorded IC (ipsilateral to the injected IC) would activate excitatory pathways arising from the multipolar and pyramidal cells in the cochlear nuclear complex (Osen 1972; Oliver 1984, 1987; Malmierca et al. 1999, 2002b), and from neurons in the lateral superior olive (Saint Marie et al. 1989) that send crossed projections to the recorded IC. The same stimulus would activate excitatory neurons projecting from the medial superior olive (Henkel and Spangler 1983), the lateral superior olive (Saint Marie et al. 1989) and the dorsal portion of ventral complex of the lateral lemniscus (Riquelme et al. 2001) that drive the ipsilateral (injected) IC from which the commissural projection originates. Binaural stimulation of the these pathways is likely to elicit a stronger influence on the recorded IC via the commissural projection than monaural stimulation alone, except in the case of IE neurons in the lateral superior olive, which might be more inhibited by binaural stimulation. Although this account oversimplifies the pathways involved, it is clear that further study is necessary to identify the contribution different inputs make to the activation of the commissural pathway.

Recent studies in vivo (Faingold et al. 1989; Zhang and Kelly 2001) and in vitro (Moore et al. 1998; Ma et al. 2002) have demonstrated that both AMPA and NMDA receptors play a role in mediating excitatory responses in the IC. Here we show that glutamate is involved in activating neurons that project across the commissure of the IC, but we cannot specify which types of receptors are blocked since KA blockade of glutamate receptors is non-specific.

The observation that commissural block leads to expansion or contraction of FRAs in different neurons, and that in some neurons changes in both directions are seen depending on the stimulus, suggests that commissural influences are mediated by excitatory, inhibitory and disynaptic pathways. This notion is in agreement with previous studies in vitro (Smith 1992; Moore et al. 1998) that reported IPSPs and EPSPs in IC neurons after electrical stimulation of the IC. Thus far the few studies available on the chemical nature of the commissural projections indicate that glutamate neurotransmission is involved (Saint Marie 1996; Zhang et al. 1998), but some evidence also points towards a GABAergic projection (González-Hernández et al. 1996). If commissural projections are both excitatory and inhibitory, the increase and decrease in FRA area we observed could be explained by monosynaptic projections. However, if the projection is solely glutamatergic, increases in FRA area might imply that commissural fibres exert their influence on neurons in the IC to which they project via an interposed GABAergic neuron. Alternatively, an increase in firing could also be explained if, owing to the position of the pipette, the KA injection does not block the commissural projection directly but rather blocks inhibitory neurons terminating on neurons with a commissural projection.

The inhibitory neurotransmitters GABA and glycine have an important role in shaping the spectral response properties of IC neurons (Yang et al. 1992; Palombi and Caspary 1996; LeBeau et al. 2001). In the light of our finding that blockade with KA can produce both increases and decreases in the size and shape of FRAs, it will be important to study how the injection of inhibitory agonists and antagonists influence commissurally mediated effects. Our current methodology does not enable us to disentangle these possibilities, but it demonstrates that neurons projecting from one IC to the other through the commissure could influence the processing of spectral information in the auditory pathway.

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