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Research Report

Differential effects of iontophoretic application of the $GABA_A$-antagonists bicuculline and gabazine on tone-evoked local field potentials in primary auditory cortex: Interaction with ketamine anesthesia☆

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ABSTRACT

γ-Aminobutric acid (GABA) is one of the main inhibitory transmitters in the central nervous system. In a recent study we have demonstrated differential effects of two iontophoretically applied $GABA_A$-blockers, bicuculline (BIC) and gabazine (SR 95531), on neuronal responses in primary auditory cortex (AI): Whereas the only effect of gabazine was to block $GABA_A$-mediated inhibition, BIC application additionally induced dose-dependent side effects, probably on calcium-dependent potassium channels. Here we investigated the effects of the two drugs on pure tone-evoked local field potentials (LFPs) in AI. In contrast to spiking activity, which reflects neuronal output, LFP are believed to mainly reflect dendritic activity and therefore neuronal input. LFPs were recorded from the left AI of anaesthetized and unanaesthetized Mongolian gerbils before, during and after microiontophoretic application of BIC and gabazine using multi-barrel glass electrodes. After the application of both drugs, a significant increase of the amplitude of the N1 component of the LFP was observed in both anaesthetized and unanaesthetized animals, but this increase was significantly more pronounced after BIC than after gabazine application, a result which corresponds to the effects on neuronal discharge rate reported earlier. In contrast, the effects of BIC and gabazine on LFP duration (prolongation) and LFP spectral tuning (sharpening) were affected by ketamine anesthesia, an effect that was not seen in the spiking data. We conclude from the data presented that the main functional role of $GABA_A$-mediated inhibition in auditory cortex is to (1) prevent over-excitation (seizures) of cortical networks and (2) to speed up cortical processing.

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Abbreviations: GABA, γ-aminobutyric acid; BIC, bicucculine; SR 95531, gabazine; LFP, local field potential; N1, first negativity of LFP; $Q_{10\ dB\_N1}$, measure of sharpness of tuning of LFP response, based on FRF_{N1}; FRF_{N1}, frequency response function of LFP response; BF_{N1}, best frequency of N1 component of LFP response; P2, second positivity of LFP; *df*, degrees of freedom

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1. Introduction

γ-Aminobutric acid (GABA), one of the main inhibitory transmitters in the central nervous system, is the major inhibitory neurotransmitter in cerebral cortex (Curtis and Johnston, 1974; Krnjeviæ, 1984; Winer, 1992). There it acts mainly on $GABA_A$- and $GABA_B$-receptors (Bormann, 1988, 2000; Chebib and Johnston, 1999). $GABA_A$-receptors mediate fast inhibitory postsynaptic potentials (Metherate, 1998; Li et al., 1996) and therefore are particularly well suited to generate or sharpen receptive field properties of cortical neurons.

In a recent study (Kurt et al., 2006), we have investigated differential effects of two iontophoretically applied $GABA_A$-blockers, bicuculline (BIC) and the pyridazinyl-GABA derivative gabazine (SR 95531), on single and multi-unit responses in primary auditory cortex (AI). We could demonstrate that, depending on the dose applied, BIC can have deleterious effects on neuronal response selectivity which do not reflect the loss of GABAergic inhibition. These effects include increased discharge rates of both spontaneous and evoked neuronal spiking activity, widening of spectral receptive fields as well as a prolongation of tone-evoked responses. We suggested that this effect may be due to non-GABAergic side effects of BIC reported in the literature which may affect neuronal discharges in a dose-dependent manner. These side effects include inhibition of GABA uptake, reduction of resting membrane conduction resulting in membrane depolarization, prolongation of calcium-dependent action potentials, paroxysmal depolarization shifts and apamin-like potentiation of burst firing (Olsen et al., 1976; Heyer et al., 1981; Johnson and Seutin, 1997). At least some of these secondary effects are thought to result from actions of BIC on calcium-dependent potassium channels (Johansson et al., 2001). In contrast, application of gabazine, although it has a higher affinity for the $GABA_A$-receptor than BIC, never led to observable side effects but only to blocking of $GABA_A$-mediated inhibition (see also Chambon et al., 1985; Heaulme et al., 1986; Hamann et al., 1988).

Here we investigated whether the deleterious effects of BIC on pure tone-evoked responses of single and multi-units in AI can also be seen on the population level of cortical activity. We therefore compared the effects of iontophoretic application of BIC and gabazine on pure tone-evoked local field potentials (LFP) in gerbil AI.

As LFP mainly reflect dendritic potentials and therefore are considered to represent neuronal input, a comparison of this report with the data presented in Kurt et al. (2006) may also allow for a differentiation of the effects of blocking $GABA_A$-mediated inhibition on neuronal input and (spiking) output, respectively. More specifically, LFP reflect both inhibitory as well as excitatory dendritic inputs (inhibitory and excitatory postsynaptic potentials, IPSP and EPSP, respectively), whereas spiking responses only reflect above threshold excitation of the neuron recorded from. Therefore, changes in LFP characteristics may be seen after blocking inhibitory dendritic inputs that are not necessarily reflected in spiking output.

2. Results

2.1. Database

All results presented are based on measurements on a total of 26 male Mongolian gerbils. Pure tone-evoked LFP were recorded at a total of 91 recording positions. Effects of application of $GABA_A$-antagonists on the N1 component of pure tone-evoked LFP were investigated at 38 recording positions in unanaesthetized animals (BIC: 27, gabazine: 11) and at 53 positions in anaesthetized animals (BIC: 17, gabazine: 36).

2.2. Drug effects on N1 spectral tuning

To characterize the spectral tuning of pure tone-evoked LFP, we used the measure of the $Q_{10\ dB\_N1}$ (cf. Experimental procedures).

Fig. 1 shows two examples of this type of analysis: It can be seen that in both cases the N1 spectral tuning became sharper under the influence of $GABA_A$-blockers, leading to higher $Q_{10\ dB\_N1}$-values, respectively.

Fig. 2 shows the population data of all recording sites tested. Here the effect could be found for the population data

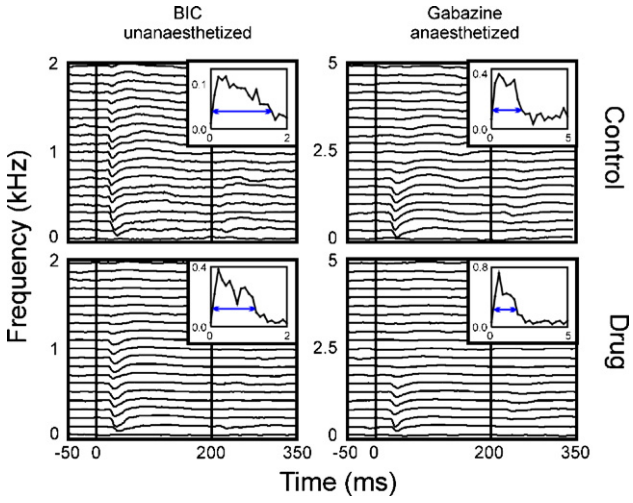

Fig. 1 – Spectral tuning of pure tone-evoked LFPs. The panels show examples of raw data as obtained in our experiments. In each panel, pure tone stimulation frequency is plotted over time. Each horizontal line represents a LFP (mean over 15 stimulus presentations) evoked by a pure tone, stimulus was present between 0 and 200 ms as indicated by vertical lines. The insets show the LFP amplitude in absolute mV as a function of stimulus frequency in kHz (=N1 frequency response function = FRF_{N1}). From these, the best frequency of the LFP response (BF_{N1}) was determined (=peak of the FRF_{N1}). As a measure of sharpness of tuning, $Q_{10\ dB\_N1}$ was defined as BF_{N1} divided by the width of the FRF_{N1} – Peak around BF_{N1} 10 dB below BF_{N1} (blue arrows). As can be seen, in both examples, tuning sharpness increased by the application of both BIC and gabazine in both anaesthetized and unanaesthetized animals.