Physiol. Res. 51(Suppl 1): S95-S104, 2002

Changes in the Acoustically Evoked Activity in the Inferior Colliculus of the Rat after Functional Ablation of the Auditory Cortex

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Summary

The role of the cortico-tectal pathways in the processing of auditory signals was investigated by recording the click-evoked responses and extracellular multiple unit activity in the inferior colliculus (IC) after functional ablation of the auditory cortex (AC) by local intracortical application of a sodium channel blocker, tetrodotoxin (TTX). Click-evoked IC responses (IC-ER) and multiple unit activity in response to tone bursts were recorded with implanted electrodes in the IC of rats lightly anaesthetized with xylazine. Neural activity was recorded before and after the application of TTX into the ipsilateral auditory cortex (AC) through three implanted cannulas in a total dose of 30 ng. The functional status of the AC was monitored by recording click-evoked middle latency responses from a ball electrode implanted on the AC. During inactivation of the AC, IC-ER amplitudes were either increased (48 % of the cases), decreased (32 % of the cases) or not evidently changed (20 % of the cases). Corresponding effects were observed in the firing rate of IC neurons. Functional ablation of the AC also resulted in a significant prolongation of the latencies of individual waves of the IC-ER. However, the discharge pattern of the multiple unit responses, response thresholds and tuning were not altered during AC inactivation. IC neural activity recovered within several hours, and maximally during 2 days. The results reveal principles of the interaction of cortico-tectal pathways with IC neuronal activity.

Key words

Auditory cortex • Inferior colliculus • Corticotectal pathways • Functional ablation • Rat

Introduction

Several anatomical studies demonstrated that the inferior colliculus (IC) and the medial geniculate body (MGB) are two of the primary targets of descending fibers from the auditory cortex (AC). The essential morphological features of this pathway are maintained among the mammalian species studied (Diamond *et al.* 1969, Warr 1975, Anderson *et al.* 1980, Adams 1980, Hashikawa 1983, Robertson 1985, Syka *et al.* 1988).

In the IC, the majority of descending fibers innervate the dorsal cortex of the IC (DCIC), although projections to the central nucleus (CNIC) and external cortex (ECIC) have also been demonstrated (Druga and Syka 1984, Faye-Lund 1985). Whereas the morphology of corticofugal pathways is well documented, their function in the processing of auditory signals has not been resolved. It has been suggested that the corticofugal fibers might play a modulating or gating role for the transmission of auditory signals through subcortical sensory systems (Herbert *et al.* 1991). Electrical stimulation of the AC was shown to produce facilitation, depression or a combination of both effects on evoked responses recorded from the IC (Syka and Popelář 1984,

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Sun *et al.* 1996), whereas inactivation of the AC in the bat reduced the auditory responses of matched FM-FM IC neurons and broadened delay tuning curves (Yan and Suga 1996). Investigators do not agree on the mechanisms underlying the observed response properties of the IC neurons. Some have advanced inhibitory mechanisms while others have suggested excitatory or facilitatory mechanisms to explain their results (Yang *et al.* 1992, Fuzessery and Hall 1996, Suga *et al.* 1997). In the guinea pig the pathways from the AC to the IC were shown to be glutamatergic (Feliciano and Potashner 1995). In behavioral studies cortical ablation was shown to primarily damage the ability to localize sound (Jenkins and Merzenich 1984) or the gap detection threshold (Ison *et al.* 1991, Kelly *et al.* 1996). The results of the foregoing studies highlight the central role of the corticofugal system in influencing the response properties of subcortical auditory neurons (IC) in the presence of acoustic signals. Hence a detailed understanding of the exact roles of the corticofugal system in auditory signal processing can improve the present level of knowledge on central auditory system function.

The aim of the present study was to investigate the changes in acoustically evoked activity (click-evoked responses and extracellular multiple unit responses) in the inferior colliculus of the rat after functional ablation of the AC by local intracortical application of the sodium channel blocker, tetrodotoxin (TTX)[1].

Methods

Eight adult rats (Long Evans), each weighing between 230 and 450 g, were used for this study. The animals were anesthetized (i.m.) with a ketamine-xylazine mixture in a dose of 37.5 mg/kg of ketamine and 5 mg/kg of xylazine. Three stainless steel cannula tubes (diameter 1 mm, length 7mm) were implanted around the circumference of the right AC through three small holes for the injection of TTX, and a ball electrode (teflon-coated platinum-iridium wire) was fixed on the middle of the AC for recording the middle latency responses (MLR). Two metal electrodes (insulated nichrome wire, diameter 0.002 inches) with a length differential of 1 mm were implanted according to stereotaxic coordinates into the peripheral parts of the ic (ipsilateral to the AC) for recording the inferior colliculus evoked responses (IC-ER) and the extracellular multiple unit responses. A reference electrode was fixed in the neck muscles. All electrodes were soldered to the connector socket, which was fixed on the skull by two stainless steel screws and acrylic resin.

The animals were rehabilitated for at least seven days. Recording of the IC neural activity was performed in a sound-attenuated and anechoic room with the rat lightly anesthetized with xylazine (0.03 ml/100 g). The rat's rectal temperature was maintained between 37.0 and 38.0 °C with a heating pad.

To examine the click-evoked responses, bipolar clicks (100 μs duration) were generated by SigGen TDT (Tucker-Davis Technologies) software, processed by a TDT D/A converter and programmable attenuator and presented to the animals from a loudspeaker (located 75 cm in front of the head of the animal) in free-field conditions in an anechoic chamber. Calibration of the sound field was performed with a Brüel and Kjaer microphone (type 4134) and Brüel and Kjaer amplifier

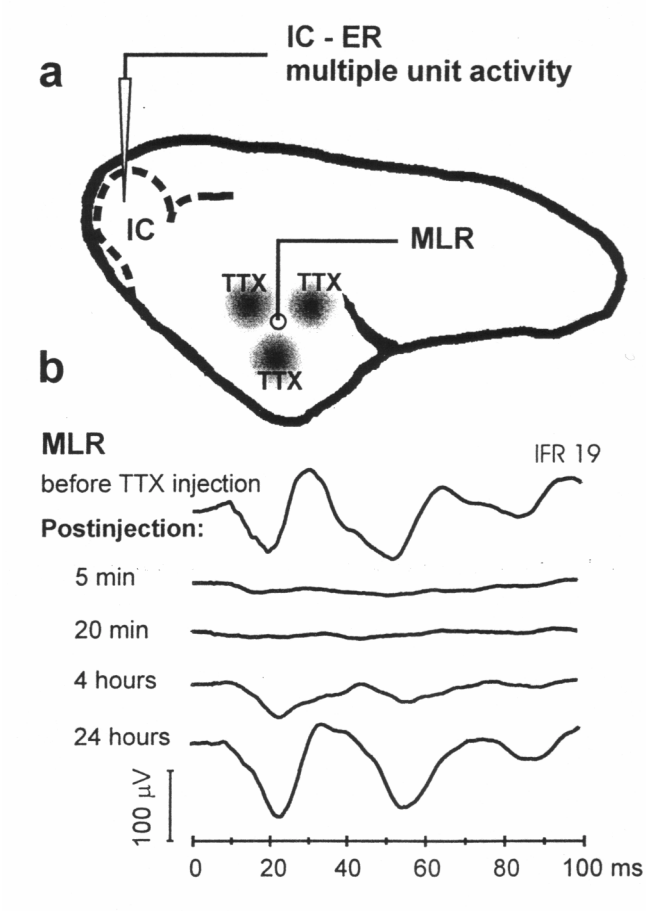

Fig. 1. *Schematic design of the experiment (a) and an example of MLR recorded in one animal (IFR 19) before and after AC inactivation by TTX injection (b).*

(type 2603). The microphone was placed in the position of the animal's head during the experiment. The signal from the electrodes was amplified by a DAM differential amplifier (gain 60 dB, filters 10 Hz-1 kHz) and processed with an A/D converter of the TDT system using BioSig software.

For evaluation of the extracellular multiple unit responses, the animals were stimulated with tone bursts at the characteristic frequency (CF), which varied in intensity levels. Tone bursts (100 ms duration, 5 ms rise/fall times) were generated by a Hewlett Packard 33120A waveform generator and shaped by a custom-made electronic switch. The multiple unit activity was preferentially recorded from the electrode with the larger spike amplitude. The signal from an electrode was amplified by a DAM differential amplifier (gain 60 dB, filters 100 Hz-10 kHz) and further processed using an intelligent interface Cambridge Electronic Design 1401plus and software Spike II. Individual spikes were isolated from multiple unit activity either by an amplitude discriminator or by Spike2 software according to templates sorting.

Before TTX application the functional status of the AC was continuously monitored by recording the click-evoked MLR from the implanted electrode. Subsequently, using a Hamilton syringe, TTX in a total dose of 30 ng (10 ng/ μl) was introduced 1 mm below the pial surface of the AC through the three cannulas so as to cover the entire surface of the AC (Fig. 1a).

The auditory stimulation and data acquisition were repeated in a graded sound intensity (SPL) and at different post-TTX injection times. In five animals the TTX injection and IC neural activity recording were repeated in a second session performed two to three weeks after the first session.

At the end of the experiment the animals were deeply anesthetized with pentobarbital (Pentobarbital Spofa, 150 mg/kg) and perfused intracardially with 10% formol. The positions of the IC electrodes were reconstructed from histological sections of the animals' brains with the aid of a stereotaxic atlas of the rat brain (Paxinos and Watson 1982).

Results

AC neural activity

The functional status of the AC was controlled by recording the click-evoked middle latency responses (MLR) with an electrode implanted on the surface of the AC approximately at the centre of the AC. As a rule, control MLR consisted of two or three waves with a total duration of 50-60 ms (Fig. 1b). Several minutes after TTX injection in the AC, the MLR waves almost entirely disappeared, and this effect lasted from several hours to three days. Full recovery of MLR amplitude was observed 1-2 days post-injection.

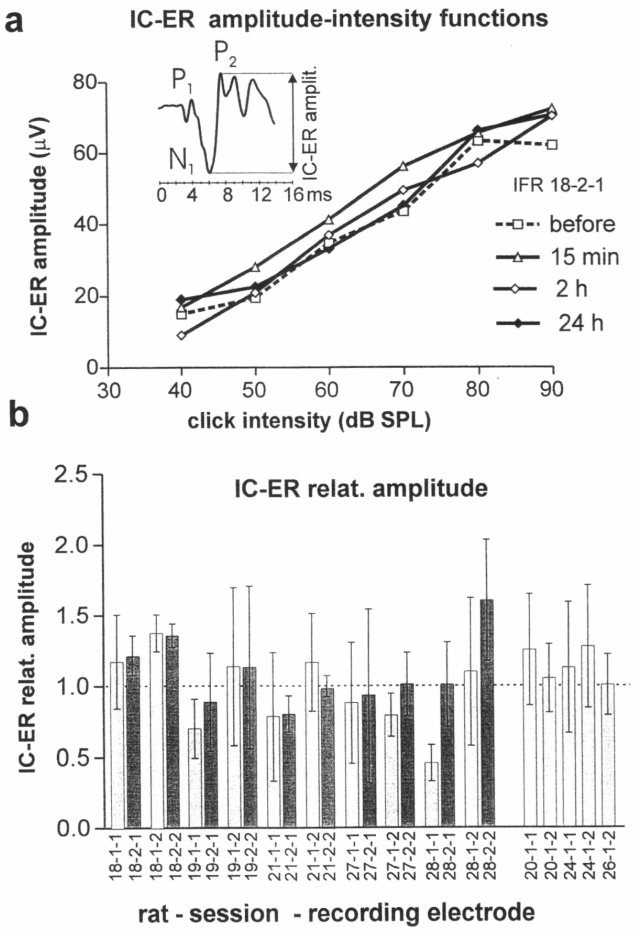

Fig. 2. *(a) An example of IC-ER amplitude intensity functions evaluated in one animal (IFR 18) before and after AC inactivation by TTX injection. The insert figure demonstrates the principle of IC-ER amplitude measurement. (b) IC-ER amplitude changes in individual animals. Each column represents an average of relative amplitudes (i.e., the ratio of amplitude value after TTX injection and control amplitude) computed for an individual stimulus intensity; vertical bars represent S.D. Labels below the columns consist of the animal number, recording session and electrode number separated by a stroke. The white columns represent the IC-ER relative amplitude measured in the first session, whereas results obtained in a second experimental session from the same electrode of the animal are shown by a dark gray.*

IC evoked responses

Recording of IC evoked responses (IC-ER) usually started 10 minutes after cortical deactivation by TTX. Responses to click stimulation were recorded with the intensity increasing by 10 dB steps alternately from both electrodes; averaged responses were stored on harddisk of the PC. Peak-to-peak IC-ER amplitude (see insert in Fig. 2) increased linearly with increasing stimulus intensity. In some animals inactivation of the AC resulted in a slight increase of IC-ER amplitudes (demonstrated in the example of IC-ER amplitude-intensity functions in Fig. 2a) or in a decrease of the response amplitudes. The changes in the IC-ER amplitude were not accompanied by any pronounced changes in the response shape or response threshold.

The IC-ER amplitudes usually recovered within several hours or days. In the bottom part of Fig. 2 are shown relative amplitude changes of the IC-ER measured from both electrodes of individual rats 10-20 minutes after TTX injection. The value of each column was obtained by averaging relative IC-ER amplitudes (i.e. the ratio of IC-ER amplitude measured before and after TTX application) calculated for all stimulus intensities used. Five animals received a second dose of TTX two weeks after the first injection. Data displayed in Fig. 2b demonstrates that AC inactivation resulted in either a small increase (48 % of the cases), decrease (32 % of the cases) or no evident change (20 % of the cases) of IC-ER amplitude. Although the changes in the amplitude were small, they were consistent and reproducible for individual electrodes in the same animal after repeated TTX injection ($r=0.616$, $p<0.095$, paired t-test).

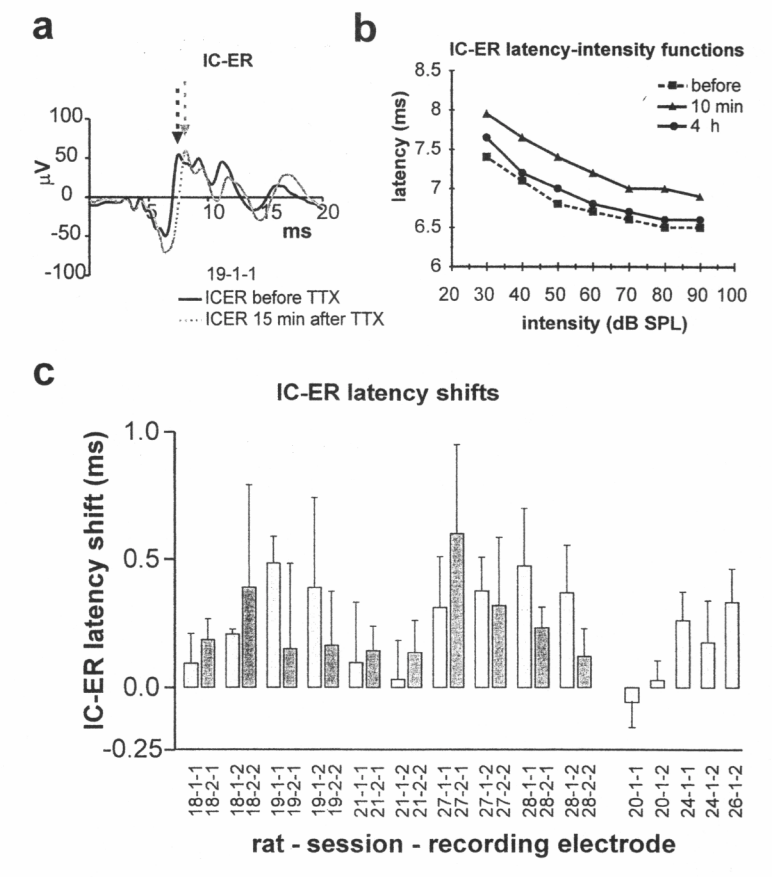

Fig. 3. *(a) An example of IC-ER recorded in one animal (IFR 19-1) with indicated latency shift after AC inactivation by TTX injection and resulting latency-intensity functions of the wave P_2 (b). (c) IC-ER latency shift measured in individual animals. Each column represents an average of latency shifts computed for an individual stimulus intensity; vertical bars display S.D. The grey and dark columns represent the IC-ER latency shift measured in the same animal during the first and second sessions.*

IC-ER latency shift

Functional ablation of the AC resulted in a prolongation of the IC-ER wave latencies. The example in Fig. 3a documents a latency shift of individual waves of the IC-ER and the P_2 latency-intensity functions. In most animals, wave latencies shorter than the latency of P_1 (which probably originated in the brainstem auditory nuclei) did not change significantly, but prolongation was typical for the latency of the N_1 and subsequent waves. As a rule, the latency value decreased with increasing sound intensity. An example of a P_2 latency-intensity function is displayed in Fig. 3b. After the TTX injection,

the latency-intensity function was shifted as intensity values were increased but was restored to the pre-TTX value several hours post-injection. In individual animals and electrodes, the average latency shift (i.e. average of latency shifts measured at individual click intensities) varied between 0.1-0.6 ms regardless of the decrease or increase in the IC-ER amplitude (Pierson correlation coefficient r=0.37) (Fig. 3c). Even though IC-ER latencies in all animals but one were significantly prolonged, the values of the latency shift observed during the first and second experimental sessions were not as consistent as the IC-ER amplitude changes (r=0.1). The IC-ER latencies also recovered within several hours or days.

IC multiple unit activity

In seven animals, one electrode from a pair was chosen for recording the multiple unit activity from the IC. At first, the frequency tuning of neuronal activity in the proximity of the electrode tip was investigated and a frequency-tuning curve (FTC) was constructed. The frequency with the lowest threshold of response, i.e. the characteristic frequency of the multiunit ensemble, was determined from the FTC. Functional ablation of the AC did not induce any change in the CF value or the shape of the FTC.

The firing rate of the IC multiple unit activity was evaluated with post-stimulus time histograms (PSTH), calculated from the responses to tone-bursts at the CF. Similarly as the amplitudes of the IC-ER, the firing rate of the multiple unit activity was either enhanced, depressed or not changed. From PSTHs evaluated at several stimulus intensities, spike-intensity functions were constructed. Examples of PSTHs and spike-intensity functions, measured in one animal before and after AC functional ablation, are presented in Fig. 4. In this example, the number of spikes in the response markedly increased forty minutes after TTX injection into the AC in comparison with pre-injection values. Because the threshold of response did not change, the AC inactivation resulted in an increased slope of the spike-intensity function. Even though the number of spikes in the response increased, the shape of PSTHs remained in principle unchanged. Two hours post-injection the response magnitude returned to pre-exposure values.

Functional ablation of the AC caused a depression of the firing rate of multiple unit responses in about half of the electrodes, whereas in the other half the number of spikes in response to auditory stimulation increased after intracortical TTX injection. In three animals, functional

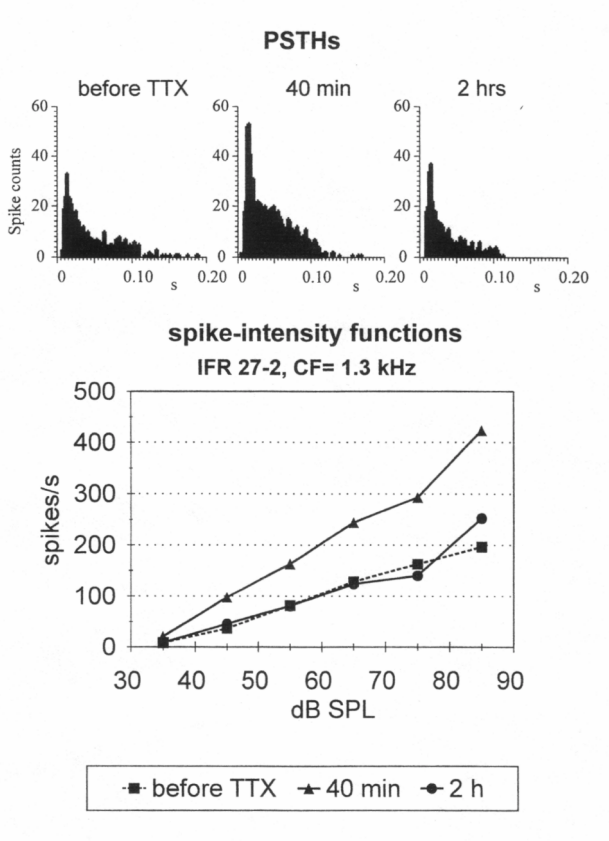

Fig. 4. *Examples of PSTHs evaluated in one rat (IFR 27) to CF stimulation at a stimulus intensity of 65 dB SPL obtained before and after TTX injection into the AC and the resulting spike-intensity functions.*

ablation of the AC resulted in more pronounced changes in the later part of the response whereas the onset part of the response was changed to a lesser extent. Such a case is documented in the example of PSTHs in Fig. 5. The recovery of multiple unit activity in this animal lasted as long as 24 hours.

Discussion

Our data demonstrate changes in neural activity in the IC after temporal functional AC inactivation by TTX. Evoked response amplitudes and multiple unit responses either increased or decreased, and the latencies of individual IC-ER waves were significantly prolonged several minutes after TTX injection. These changes lasted for several hours and recovered after 24 to 48 hours. On

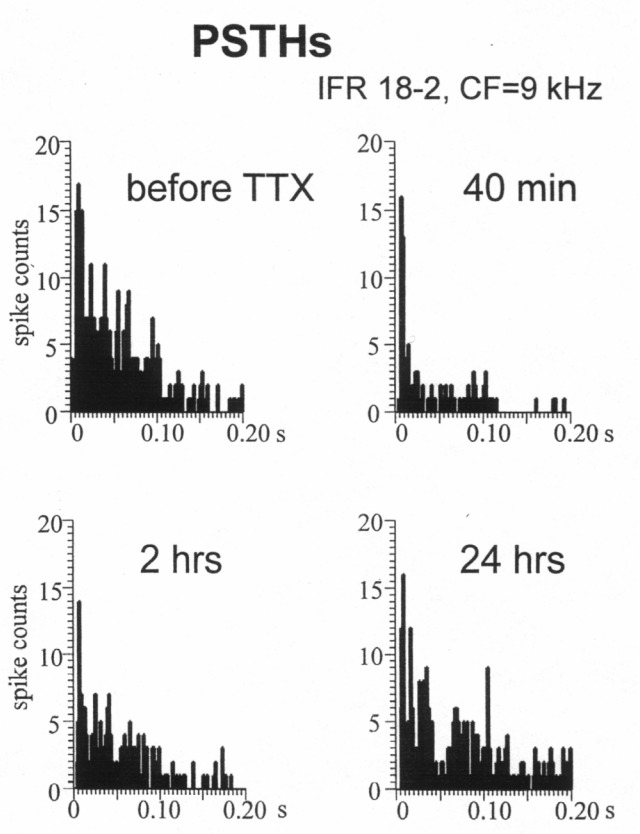

Fig. 5. *Examples of PSTHs evaluated in one rat (IFR 18) to CF stimulation at a stimulus intensity of 65 dB SPL obtained before and after TTX injection into the AC.*

the other hand, the thresholds of responses, the CF value and the shape of the PSTHs were not markedly altered after functional ablation of the AC. Previous behavioral studies exploring the role of the AC in auditory perception performed in different animal species have yielded contradictory results. Ablation of the AC in the cat, ferret and squirrel monkey resulted in severe sound localization inability, hearing loss, impairment of frequency discrimination or other hearing deficits (Neff 1968, Heffner and Heffner 1989, Jenkins and Merzenich 1984). In contrast, studies with the albino rat revealed little impairment in sound localization (Kelly 1980) and no obvious abnormality in conditioned autonomic responses to auditory stimuli (LeDoux *et al.* 1984) following bilateral ablation of the AC. The relative lack of permanent behavioral deficits after lesions of the AC in the rat raises the question of the functional significance of the cortex for hearing.

The aim of the present paper was to study the role of the efferent auditory system descending from the AC to the IC. Instead of permanent cortical lesions, the method of reversible temporal inactivation of the AC by TTX injection was used. TTX is a powerful sodium channel blocker, which has been used in numerous behavioral studies (Rothfeld *et al.* 1986, Bureš and Burešová 1990, Zhuravin *et al.* 1994) because of the advantages it holds over permanent surgical lesions. Zhuravin and Bureš (1991) have previously demonstrated that impulse transmission and conduction induced by TTX injection are blocked in a spherical volume of brain tissue about 3 mm in diameter and that this effect lasts 2 hours and slowly decays over the subsequent 20 hours. The extent of the AC in the rat is approximately 5-6 mm. Hence, three doses of TTX injected through triangular coordinates were just enough to cover the whole extent of the AC, which was confirmed by the disappearence of AC evoked potentials.

The physiology of the descending pathways from the AC was previously studied in experiments using electrical stimulation of the AC. Watanabe *et al.* (1966) and Andersen *et al.* (1972) reported that electrical stimulation of the AC produced both excitation and inhibition of single units in the medial geniculate body. Similarly, Syka and Popelář (1984) analyzed the role of the corticocollicular pathway in the rat. These authors found that electrical stimulation of the AC evoked in half of the neurons either a brief burst of excitation of IC neuronal activity, suppression of spontaneous or sound-evoked activity or a combination of both effects, i.e. short-latency excitation followed by subsequent inhibition. Similar effects of electrical stimulation of the AC on the IC neurons were obtained by Torterolo *et al.* (1998) in the guinea pig.

In another experiment, Syka *et al.* (1988) studied the depth profile of gross electrical responses in the IC evoked either by acoustical stimulation or by electrical stimulation of the AC. Whereas acoustically evoked responses dominated in the central part of the IC, electrical stimulation of the AC produced responses mainly in the part of the IC near its surface. Similarly, click-evoked responses recorded in the peripheral parts of the IC were significantly suppressed by a preceding electrical pulse to the AC. This finding is consistent with the projection of afferent fibers to the central IC nucleus, whereas external and dorsal cortices of the IC are targets of descending cortical fibers (Druga and Syka 1984, Faye-Lund 1985, Huffman and Henson 1990).

Taking the above-mentioned data into account, in the present work electrodes for recording of the IC activity were preferentially implanted in the peripheral part of the IC, i.e. in the dorsal and external cortices of the IC, where the changes in neural activity induced by AC inactivation were thought to be more pronounced

than in the central nucleus of the IC. In agreement with the results of electrical stimulation of the AC, after functional ablation of the AC suppression, enhancement or no effect on neural activity in the IC were observed. Even though the changes in the IC-ER amplitudes and multiple unit responses were small, they were related to the functional status of the AC and not to incidental fluctuation of neuronal activity within the IC. Repeated TTX injection into the AC of the same animal during two experimental sessions resulted in almost identical, reproducible IC-ER amplitude changes. Further, examination of several PSTHs revealed that the onset part, which represents the afferent signal to the IC, was less affected than the sustained part of the PSTH, which is thought to indicate the processing of information within the IC.

The differential actions on the IC may be seen as the resultant effect of the modulatory role of the corticofugal system on the excitatory, inhibitory, and facilitatory neural interactions that commonly take place in the central auditory system. It has been proposed that the corticocollicular projections could modulate auditory information through inhibitory GABAergic cells present in the IC (Faingold *et al.* 1991, Oliver *et al.* 1994, Mugnaini *et al.* 1995) and excitatory glutamatergic descending fibers (Feliciano and Potashner 1995). Jen *et al.* (1998) previously suggested a dual corticofugal pathway to explain the observed differential effects in bats. They concluded that corticofugal fibers terminating on the central nucleus of the IC (CNIC) represent corticocollicular facilitation while pathways for corticofugal inhibition are represented by excitatory projections from the AC to the external nucleus of the IC, which then sends inhibitory inputs to the CNIC neurons. In our experiments, no data were observed from the CNIC because our experiments were designed to record neural activity preferentially from the peripheral parts of the IC. However, our results did not document any evident differences between the external and dorsal cortices of the IC. Suga and coworkers (Riquimaroux *et al.* 1992, Zhang and Suga 1997, Zhang *et al.* 1997) studied the effects of inactivation of the corticofugal system on the auditory responses of subcortical neurons in the moustached bat. They found that focal cortical inactivation by a local anesthetic, lidocaine or muscimol, decreased or increased responses of the IC neurons, changed their CF value and changed the delay-tuning in specialized neurons. In our experiments, the temporal inactivation of the whole AC resulted in changes of response magnitude or latencies of IC-ER waves, but we did not observe any shift in CF or changes in tuning curves. The function of the corticocollicular pathway may be species-specific and hence the results of Jen *et al.* (1998) and Suga's group measured in the bat differ from neural data obtained in the rat.

Examination of the response latency in our data demonstrated that latencies of individual waves of IC-ER were substantially prolonged during AC inactivation, whereas latencies of early waves (shorter than 5 ms), which are thought to originate in the brainstem auditory nuclei, were not changed. We are at present unable to ascertain the molecular processes underlying this observation. It has been demonstrated previously that pathways descending from the guinea pig AC to the IC are glutamatergic (Feliciano and Potashner 1995). Large numbers of NADPH-d-positive cells, which indicate a high incidence of nitric oxide in the structure, were also detected in the peripheral parts of the IC (Druga and Syka 1993). The NADPH-d activity in the ipsilateral IC was significantly reduced in rats with an AC lesion (Druga *et al.* 1999). The prolongation in the IC-ER wave latencies may be due to metabolic changes involving neurochemical mediators of the IC. Molecular techniques may shed more light on the underlying mechanism responsible for this observation.

Appendix

[1] In the second year of my (JS) study of medicine, I decided that my knowledge of brain anatomy was sufficient to start some serious study of brain function. I was looking around to find a teacher who would introduce me into the secrets of brain investigation. One of my teachers at that time, by himself a very talented histologist, suggested that I contact Jan Bureš in the Institute of Physiology. In fact he picked up the telephone and called him. This was the moment that started my acquitance with Jan, which continues until now. Jan was, when it happened in 1961, already world famous thanks mainly to his elegant studies of spreading depression. With his wife Olga, they paved the modern way of behavioral studies of memory and learning in the rat. In his laboratory were always many Czech and foreign students as well as many distinguished visitors from all over the world. This was an excellent opportunity for a young science apprentice to learn about the state of the art in brain research (the term neuroscience was not common at that time) in the world. Jan was a great teacher but he expected the apprentice to be highly motivated and able to solve some simple tasks without

the help of others. In the sixties electrophysiological methods spread throughout the world and the first LINC and LAB computers started to be available. Jan acquired at that time probably the first LINC computer in the so-called socialist countries. As a student in his laboratory, I had to master not only the knowledge of amplifiers, transistors and later integrated circuits, but also to learn computer programming, fortunately only in Basic. So when George Gerstein published his cross-correlation techniques for the assessment of the interaction of nerve cells, soon they were available in Prague. Gerstein was, by the way, one of the frequent visitors in the Bureš laboratory. For beginners in electrophysiological studies, a vade mecum Electrophysiological Methods in Biological Research was of great help, written in the sixties by Bureš, Petrán and Zachar, published in English and translated into several languages. It was widely used all over the world and in many aspects has not yet been surpassed. The training in the Bureš laboratory together with the unique climate resulted in the fact that already before the end of my medical studies, we published together with Eva Fifková my first scientific paper in Experimental Neurology. The topic was, of course, spreading depression. I wish to all beginners in the neuroscience field today to have such great luck in their life to start their career with such an ingenious teacher, scientist and great friend as is Jan Bureš.

Acknowledgements

This work was supported by Grant No. 4747-3 of the Ministry of Health of the Czech Republic.

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