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EFFECTS OF AN HYPOXIA AT 5% OXYGEN ON GLOBAL ELECTROPHYSIOLOGICAL RESPONSES FROM NORMAL AND HYDROPIC EARS OF A WAKE GUINEA PIGS

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SUMMARY

In the continuation of our studies on the involvement of blood supply deficiencies in various experimental pathologies of the inner ear we have conducted a study on the effects of transient hypoxia on normal and hydropic ears. In the same study we investigated the possible protective effects of an anti-ischemic drug. All experiments were conducted on awake guinea pigs warranting a normal physiological functioning of the circulatory system. Global electrophysiological responses from the inner ear were monitored: cochlear microphonic, summing potential and auditory nerve compound action potential. In normal ears hypoxia induced a threshold elevation at all frequencies thus affecting the whole cochlea, and also very large diminutions of action potential amplitude evoked at high intensity level exclusively in response to a high frequency. Hydropic ears presented an hypersensitivity to anoxia, their action potential amplitude being affected at more stimulus frequencies and presenting a much slower recovery process, but their threshold elevations were similar to those of normal ears. The drug treatment limited the decrease of action potential amplitude in normals, but no such effect was observed for hydropic ears.

RESUME

Dans la continuation de nos études sur l'implication de troubles vasculaires dans différentes pathologies expérimentales de l'oreille interne nous avons étudié les effets d'une hypoxie transitoire sur des oreilles normales et hydropiques. Dans la même étude nous avons examiné les effets protecteurs éventuels d'un médicament anti-ischémique. Les expériences ont été réalisées sur des animaux éveillés ce qui garantit un fonctionnement normal des contrôles circulatoires. Les réponses électrophysiologiques globales de l'oreille interne, microphonique, sommation et potentiel nerveux, ont été suivies en continu. Sur les oreilles normales l'hypoxie a produit une élévation de seuil à toutes les fréquences affectant donc l'ensemble de la cochlée, mais aussi une très forte diminution du potentiel nerveux évoqué à forte intensité par une fréquence aigue exclusivement. Les oreilles hydropiques ont présenté une hypersensibilité à l'anoxie, le potentiel nerveux étant affecté à plus de fréquences de stimulation et montrant une récupération plus lente, mais les élections de seuils ont été semblables à celles observées sur les oreilles normales. Le traitement par médicament a limité la diminution du potentiel nerveux sur les oreilles normales mais on n'a pas observé d'effet sur les oreilles hydropiques.
INTRODUCTION

Deficiencies in blood supply are extremely widespread in human population especially in the elderly. Involvement of vascular insufficiencies to the inner ear induced experimentally have long been known to produce drastic functional alterations (1,2). An involvement of vascular disturbances in various hearing disorders is often suspected and vasoactive drugs are largely used in the treatment of numerous hearing disorders. However even in experimental conditions measurements of cochlear blood flow and composition are technically cumbersome and the validity of the obtained data is always questionable due to the physiological alterations induced by the experimental procedures (3). In a series of recent experiments we undertook to study in awake guinea pigs, thus without doubt as to the normal physiological functioning of blood circulation system, electrophysiological alterations induced by some vasoactive drugs. Our studies involved not only normal ears but also ears affected by different experimental pathologies. We thus provided evidence of efficacy of noradrenalin related drugs on the ototoxicity of high doses of aspirin thus supporting the idea of involvement of the sympathetic innervation of the cochlea (4). In another study we detected some beneficial but limited effects of a long term treatment with a drug having some anti-ischemic properties on hydropic ears of guinea pigs (5). Such positive results lead us to pursue our experimental studies on the effects of vasoactive drugs on pathological ears in the awake guinea pig. In this perspective we report here on the effects of transient hypoxia on electrophysiological responses from normal and hydropic cochleas, in the same study we have included the test of a drug with anti-ischemic properties (6).

MATERIALS AND METHODS

Adult pigmented guinea pigs were used in this study. Two groups were constituted: a group of five normal animals to obtain normative data and a group of eight animals which had been operated to induce endolymphatic hydrops. Hydropic animals were taken after three months at the end of the first phase of hearing loss development when the very high frequencies start to show some loss but threshold at the best absolute sensitivity is still normal (7).

During a test session of hypoxia animals were put in a restraining box and their nose introduced in a little mask in which a tube delivered a mixture of 5% oxygen and 95% nitrogen. Electrophysiological recordings were made every ten minutes or less during an hour and a half. A test session started with half an hour of normal breathing, then the hypoxic mixture was delivered during half an hour and finally, the session ended with a half-hour of normal air breathing. Audiograms were taken at the beginning of the test session, during hypoxia and at the end of the test session, stimuli at octave frequencies from 0.5 to 32 kHz were used. Every ten minutes recordings of action potential, summating potential and microphonic responses were taken and measured in response to tone bursts of 16, 8 and 2 kHz presented at a level of 80 dB SPL.

All animals were given daily during seven consecutive days an oral dose of 2.5 milligrams of trimetazidine per kilogram of body weight. Immediately after the last drug administration the animals underwent another test session.

RESULTS

It was found that, as expected, the normal ears reacted to hypoxia with a decrease of action potential amplitude at the high frequencies and threshold elevations at all frequencies. Simultaneous alterations of summating potentials and to a lesser extent of microphonic potentials were also observed. A large interindividual variability being present in the amplitude of responses for the different potentials, their values were expressed as a percentage of the amplitude observed just before hypoxia was started. In figure 1 are presented variations in amplitude of the compound action potential in response to the 16 kHz tone burst for all the animals and the two test sessions. It can be seen that at the beginning of hypoxia a very rapid decrease led to almost null values, but within five minutes of the hypoxia which lasted thirty minutes a considerable recovery of about forty percent occurred, and at the end of the session recovery was around eighty percent.

At variance the hydropic animals exhibited less recovery and for half of them at the end of the session action potential amplitude was between zero and fifty percent. At stimulus frequencies of 8 and 2 kHz almost no variation of action potential were observed for normal ears whereas in hydropic ears for the 8 kHz stimulus a transient decrease of about thirty percent occurred. These differences between normal and hydropic ears in response amplitude at high intensities were not associated with clear differences in threshold, indeed for all ears threshold elevations of around twenty dB were observed at all frequencies.

As concerns the drug treatment we observed some beneficial effects on normal ears but not so on hydropic ears. In figure 1 comparison of results from test 1 and test 2 shows that for normals during test 2 the minima of amplitude decrease reached only twenty to forty percent, no such effect was apparent for the
Amplitude variations of the compound action potential of the auditory nerve (in response to a 16 kHz burst at 80 dB SPL) during test session of hypoxia (5% O2 - 95% N, starting at 30 and ending at 60 minutes). Both for the five control and eight hydropic ears, test 1 occurred before and test 2 just after a one-week treatment with a drug having anti-ischemic properties.
hydropic ears as seen on the same figure 1. No other difference in response amplitude or threshold elevation was seen between test 1 and test 2 neither for the normals nor for the hydropic ears.

DISCUSSION
In the data presented here on normal ears on hypoxia, it was somewhat surprising to note that changes observed at high intensity were restricted to high frequencies whereas at low intensities (threshold) all frequencies were affected. This indicates two mechanisms of action of hypoxia: one acting all along the cochlea probably on outer hair cells, and a second one affecting in particular the cochlear base at high intensities and probably linked to inner hair cells. A few previous studies reported alterations of cochlear action potential in response to high intensity stimuli and dissociated from threshold changes, they concerned sympathectomy (8) and NMDA-type glutamate neurotransmission (9). At a cellular level alterations induced by hypoxia start with ATP decrease but come to affect all metabolic processes, including neurotransmission (10). We speculate that threshold elevations could be associated with overall energetic (ATP) decrease leading to diminution of endolymphatic resting potential. Action potential changes at high intensity and at cochlear base could reflect neurotransmission disturbance: afferent, efferent or sympathetic.

The data reported here indicate from hydropic ears demonstrate an hypersensitivity to hypoxic conditions which affects the basal part of the cochlea. Indeed clear differences between normal and hydropic ears were observed in action potential and summing potential in response high intensity 16 and 8 kHz tone bursts. An hypersensitivity of the base of hydropic cochleas to loud sounds has also been demonstrated recently (11). Both hypersensitivities may originate from a similar dysfunction likely related to abnormal metabolic fatigue under long lasting stress.

The beneficial effects of the drug restricted to changes at high frequencies and high intensity, since no effect was observed on thresholds, relates to the second mechanisms indicated above linked to inner hair cell function. The absence of effect of the drug on hydropic ears suggest they lack energetic reserves or regulatory processes.

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REFERENCES