A functional and histological study of the combined effects of gentamicin and aminooxyacetic acid on the organ of Corti of the guinea pig*,**

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Summary. Aminooxyacetic acid (AOAA) is a transaminase inhibitor that has been shown to protect the inner ear from loud noises. This study was done to determine if it can also protect against the cochleotoxic action of gentamicin. Four groups of guinea pigs were injected with gentamicin in doses approximating a clinical therapeutic dose and then in ototoxic doses. Thereafter animals were treated with parenteral AOAA. The effect on hearing was investigated using Preyer's reflex measurements. All animals were sacrificed and their cochleas were examined histologically using the surface preparation technique and mid-modiolar semithin sections. Histocochleograms were plotted to compare the effects of treatment in the animal groups. There was no difference seen among the groups tested. Cochlear damage was nearly equal in all animals, and AOAA was not found to protect the cochlea against gentamicin-induced ototoxicity of gentamicin. The mechanism of the ototoxicity produced is discussed on the basis of the findings. Additionally, hair cell degeneration was studied after therapeutic doses of gentamicin. Changes seen were found to be equal to or less than 5% of the hair cells and were scattered throughout the entire cochlea.

Key words: Gentamicin – Ototoxicity – Aminooxyacetic acid – Cochlea – Histology

Introduction

Aminooxyacetic acid (AOAA) or carboxymethylamine hemihydrochloride (Sigma, St. Louis, Mo., USA) is known to be an inhibitor of several transaminases [9]. Kuriyama et al. [12] in 1966 showed that AOAA can protect against convulsions induced by chemical agents and electroshock. This activity was found to be associated with an increase in the brain gamma-aminobutyric acid (GABA) and resulted from the inhibition of GABA aminotransferase, which normally destroys GABA [14]. Bobbin and Guth [2] have shown that AOAA decreases the amplitude of the auditory nerve compound action potential elicited in response to clicks in anesthetized cats. Other studies from their laboratories demonstrated that AOAA produces a reversible increase in the hearing threshold of guinea pigs as measured by Preyer’s reflex [3]. Bobbin and Gondra [1] later found that AOAA caused a reduction in the endo cochlear potential by AOAA and suggested that the stria vascularis is one of the sites of AOAA’s action in the cochlea. Tasaki and Spyropoulos [16] previously showed this structure to be the source of the endo cochlear potential.

In a series of experiments, Bobbin et al. [4] exposed guinea pigs to intensive sound and found that hair cell damage was reduced when animals were injected previously with AOAA. As a further application of these studies the aim of our present investigation was to examine morphological and functional changes in the cochleas of guinea pigs after animals were injected with various doses of gentamicin and to determine if pretreatment with AOAA could prevent gentamicin-induced ototoxicity.
**Materials and methods**

Healthy colored young guinea pigs weighing 350–500 g were used. The animals were separated into six groups, each with at least five animals. There were two control groups: one was injected subcutaneously with physiological saline and the other was treated with AOAA 20 mg/kg per day for 15 days. Another two groups were injected with gentamicin 8 mg/kg per day for 15 days; the animals in one of these groups also received AOAA 20 mg/kg per day. The last two groups were injected with toxic doses of gentamicin 100 mg/kg for 15 days, with one group receiving AOAA in addition.

Preyer's reflexes were measured using an Atlas audiometer at frequencies of 2–8 kHz before and after the course of the injections given. All animals were sacrificed 1 week after the last injection. Hair cell damage in some cochleas was studied by the surface preparation technique as described by Engström et al. [5, 6] and Hawkins [8]. The rest of the cochleas were fixed with Karnowsky solution and osmic acid, dehydrated, and embedded in araldite, as described by Galic and Helms [7]. The embedded cochleas were studied either as modiolus semithin sections or after doing modified surface preparations as described by Spoendlin and Brun [15]. The hair cell population was counted and the number of damaged cells was determined. Histocochleograms were presented in two ways: first showing the percentage of hair cell damage in each 1 mm along the basilar membrane; second, as a diagram of selected areas from each representing about 120 hair cells to show the pattern of degeneration.

**Results**

The animal group given saline alone showed no changes in Preyer's reflex threshold after the course of the injections. The hair cell population was totally normal in this group.

The group treated with AOAA showed no changes in Preyer's reflex threshold 48 h after the course of injections. The hair cell population was normal. However, single injections of AOAA caused temporary increases in the Preyer's reflex threshold when measured 0.5 and 1.5 h after injections (Fig. 1) and was then normal after 24 h.

Preyer's reflex measurements done in animals injected with gentamicin 8 mg/kg per day showed an average hearing loss of 4 and 10 dB at 2 and 4 kHz, respectively (Fig. 2). Those animals also injected with AOAA showed average hearing losses of 0 and 3 dB at 2 and 4 kHz. The difference between the two groups did not exceed 4–7 dB. Animal groups injected with gentamicin 100 mg/kg per day lost complete Preyer's reflexes after the 15-day course, whether or not they were also injected with AOAA.

Histological examinations of all animals injected daily with 8 mg/kg gentamicin showed similar degrees and patterns of hair cell degeneration, whether or not injected with AOAA (Fig. 3). The degeneration was scattered over the entire cochlea and did not exceed 5% of the hair cells per millimeter. The outer hair cells were mainly affected and slightly more involved the outermost row of cells.

Inner hair cell degeneration was seen to some degree in the upper turns of the cochleas. The hair