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Memantine Suppresses the Glutamatergic Neurotransmission of Mammalian Inner Hair Cells

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Abstract
The glutamatergic synapses between inner hair cells and afferent neurons seem to be involved in pathophysiological conditions of the cochlea. The excessive release of glutamate from inner hair cells during noise trauma and ischemia affects the afferent neurons. It is possible that in tinnitus outer hair cell or inner hair cell dysfunction or damage leads to an altered spontaneous release of glutamate from inner hair cells. Thus, the pharmacological modulation of glutamatergic neurotransmission could be of great value in the therapy of certain inner ear diseases. Recently, it has been discovered that the spasmolytic drug memantine has antiglutamatergic properties. As a possible drug for inner ear diseases, we were interested in the action of memantine on the neurotransmission of inner hair cells. With the aid of microiontophoretic techniques we were able to show a strong depressing effect on spontaneous activity as well as on glutamate-induced activity. This effect seems to be mediated by a blockade of N-methyl-*D*-aspartate (NMDA) receptors as memantine showed a strong inhibiting effect on NMDA-induced activity but not on AMPA-induced activity. These results recommend memantine for the treatment of inner ear diseases, e.g. especially tinnitus.

Introduction

In the mammalian cochlea glutamate seems to mediate the neurotransmission between inner hair cells (IHCs) and the auditory nerve dendrites [1, 2]. During excessive release glutamate can be neurotoxic to the postsynaptic neurons [3]. This 'excitotoxicity' has been discribed for the cochlea and seems to play a role in the pathology of ischemia and noise trauma [4]. Moreover, it seems to us that in tinnitus patients various cochlear dysfunctions like outer hair cell or IHC disturbances could lead to an altered spontaneous release of glutamate from IHCs. This would cause a changed spontaneous activity of the afferent neurons which has been proposed to account for tinnitus [5, 6]. Thus, in inner ear diseases like noise trauma, sudden hearing loss or tinnitus, a modulation of the glutamatergic neurotransmission could be a promising new therapeutic strategy [7, 8]. As all different subtypes of ionotropic glutamate receptors, N-methyl-*D*-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) or kainate receptors, contribute to the glutamatergic neurotransmission of IHCs [2], most of

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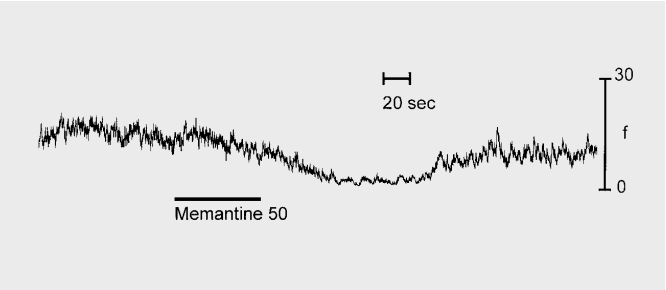

Fig. 1. Reversible suppressing effect of memantine (50 nA) on the spontaneous firing of an afferent fiber of a IHC. Note that the activity is not blocked totally. f = Frequency.

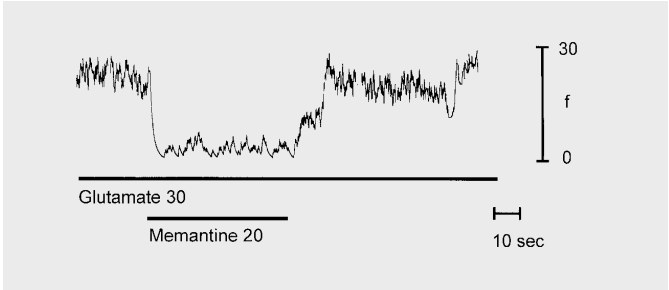

Fig. 2. Blocking effect of memantine (20 nA) on the induced firing of an afferent fiber under permanent application of glutamate (30 nA). f = Frequency.

the ionotropic glutamate receptor antagonists are possible drugs for inner ear diseases. Recently it has been discovered that the known antiparkinson and antispastic substance memantine (1-amino-3,5-dimethyl-adamantane) acts as a NMDA receptor antagonist [9, 10]. Although used for more than 10 years in the treatment of Parkinson's disease [11] and dementia [12], its influence on cochlear function has not been investigated until now, although this site of action has been discussed earlier [7, 8, 13]. The aim of this study was to establish the effect of memantine on the neurotransmission of IHCs.

Methods

Five femal pigmented guinea pigs (600–870 g) were anesthetized with a combination of xylazine (0.4 ml/kg; Rompun, Bayer, Leverkusen, Germany) and droperidol/fentanyl (Innovar-Vet; 1.3 ml/kg; Pitman-Moore, Mundelein, Ill., USA). Additional low doses were administered periodically to assure a constant deep level of anesthesia. Body temperature was monitored and maintained within physiological limits. After tracheotomy to allow artificial respiration during the experiment, the auditory bulla was approached ventrolaterally and opened. With the aid of a stereoscopic microscope a small opening was drilled in the cochlear bone right over the pigmented stria vascularis and the ligamentum spirale of the third or fourth turn. After fixation of the animal a five-barrel glass microelectrode with a tip diameter between 2 and 3 µm was inserted through the basal border of the stria vascularis and then driven almost parallel to the tectorial membrane. The subsynaptic region was reached at a depth of about 200–280 µm as indicated by typical phasic activity. Using a 2 *M* NaCl-filled barrel, recording of the extracellular action potentials was performed with standard electrophysiological equipment, displayed on-line via an oscilloscope and printed out with a thermoprinter. For later analysis data were additionally recorded on an audiotape.

Substances applied with appropriate anionic or cationic currents through the other four channels of the microelectrode included: *L*-glutamic acid (Sigma, 1 *M*, pH 7.5, adjusted with NaOH), NMDA (Sigma, 0.1 *M*, pH 8, ajdusted with NaOH), AMPA (Tocris, 0.01 *M*, pH 8, adjusted with NaOH) and memantine-HCl (3,5-dimethyl-1-adamantamine hydrochloride, RBI, 0.005 *M*, pH 3.8, adjusted with HCl).

Results

In a first set of experiments we tested the action of memantine on the spontaneous firing of afferent dendrites of IHCs. Spontaneous firing was low ranging from 2 to 17 Hz. Memantine exhibited a strong suppressing effect on spontaneous firing in all units tested (fig. 1). This inhibition was always reversible. A total blockade of spontaneous firing could not be observed, but in one experiment the blockade lastet over 15 min.

A second set of experiments were performed to establish the effect of memantine on glutamate-induced firing of afferent dendrites. The iontophoretic application of glutamate enhanced the firing rate of afferent dendrites. Memantine could reversibly inhibit this glutamate-induced firing in all units tested (fig. 2).

In a third set of experiments we were interested in the glutamate receptor subtypes responsible for these effects. We induced the firing of afferent dendrites with NMDA or AMPA. Both glutamate agonists showed a stimulating effect on the activity of afferent dendrites of IHCs. Memantine applied iontophoretically could only inhibit NMDA-induced firing, while AMPA-induced firing was unchanged as shown in figure 3. Again, this inhibiting effect of memantine on NMDA-induced firing was reversible in all units tested.

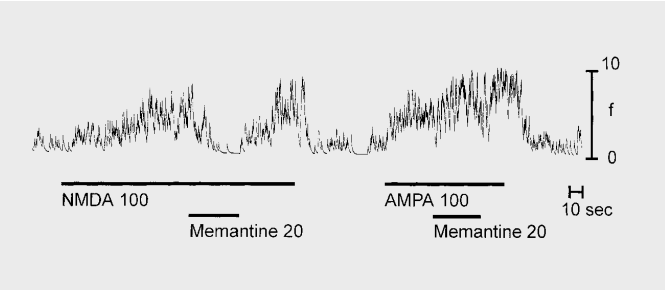

Fig. 3. Original recording of an afferent fiber which is first activated by NMDA (100 nA) and secondly by AMPA (100 nA). The application of memantine (20 nA) has a blocking effect on NMDA-induced activity, while the AMPA-induced activity was unchanged under memantine. f = Frequency.

Discussion

The results of our study clearly demonstrate the potent but reversible inhibiting effect of memantine on spontaneous as well as on glutamate-induced firing of afferent neurons of cochlear IHCs. In addition, these antiglutamatergic effects of memantine on the neurotransmission between IHCs and the primary auditory neurons are mediated by a selective blockade of NMDA receptors. This is demonstrated by the fact that memantine can suppress NMDA-activated firing but is not able to inhibit the AMPA-induced firing of afferent dendrites. Thus, memantine acts as a NMDA receptor antagonist at the glutamatergic synapses of IHCs.

To our knowledge, this is the first report on the action of memantine in the mammalian cochlea. The NMDA antagonistic properties of memantine have been discovered a few years ago [9, 10] and have been confirmed in subsequent studies [14–16]. The protective effects against glutamate-induced neurotoxicity and the antihypoxic properties of memantine in the central nervous system have been demonstrated in vitro and in vivo [14, 17–19].

The NMDA-antagonistic action of memantine at the level of the glutamatergic synapses of cochlear IHCs strongly recommends memantine as a drug for certain inner ear diseases: in case of excessive release of glutamate from IHCs during noise trauma and ischemia (which might occur in sudden hearing loss) damage to the postsynaptic afferent neurons can be observed [4]. Thus, the potent blockade of the glutamatergic neurotransmission of IHCs by memantine could be of great therapeutic value in these situations.

Cochlear dysfunction at the level of outer hair cells, IHCs or tectorial membrane could lead to a changed spontaneous release of glutamate from the IHCs. In tinnitus, altered neural activity has been suggested [5, 6]. Therefore it seems reasonable to postulate a changed spontaneous release of glutamate from the IHCs in patients with cochlear tinnitus. Thus, the suppression of the spontaneous activity of afferent neurons by memantine as shown in this study could be an important mode of action in the cochlea that strongly recommends this drug for the treatment of tinnitus.

Memantine has been shown to be safe and well tolerated even during long use in the treatment of Parkinson's disease [11], dementia [12] and other psychiatric disorders [20]. No severe side effects have been reported and it has been shown that the concentration of memantine found in the cerebrospinal fluid during therapeutic use is sufficient to block NMDA receptors [21]. These experiences should be transferred to a new therapeutic concept for the treatment of tinnitus.

Conclusions

Memantine is a safe and well-tolerated antiglutamatergic drug that is effective in the mammalian cochlea. The NMDA antagonistic action of memantine is able to inhibit the spontaneous as well as the glutamate-induced firing of afferent dendrites of cochlear IHCs. Thus, memantine can be recommended for the treatment of inner ear diseases, especially for the treatment of tinnitus, as suggested earlier [7, 8].

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