Original Article

Glutamate receptor antagonist and neurotrophin can protect inner ear against damage

DUAN Mao-li[1,2,3,4]

1 Department of clinical neuroscience, 2, Department of Otolaryngology,
3 Department of Audiology, Karolinska Hospital, 171 76 Stockholm, Sweden
4 Department of Otolaryngology, Affiliated Hospital of Anhui Medical University, China

Abstract In this study, I focused on finding a mean of protecting against hearing loss. By infusing the cochlea with the neurotrophin factor, NT-3 alone or combined treatment with MK 801, a NMDA receptor antagonist I found hearing loss was attenuated and spiral ganglion neuron loss was nearly totally protected indicating that the importance of the combined treatment of NT-3 and NMDA receptor antagonists in the treatment of hearing disorders.

Key words glutamate, NMDA receptor, NT-3, spiral ganglion neuron, hearing loss, cochlea, inner ear

Introduction

Glutamate excitotoxicity

It has long been known that the excitatory amino acid L-glutamate possesses an excitotoxicity on neurons in the central nervous system[1, 2]. In the cochlea, Puel et al demonstrated that glutamate had excitotoxic effects on the afferent dendrites under the inner hair cells causing swelling of radial dendrites[3, 4]. However, glutamate had no such effect on the dendrites under the outer hair cells. It has been found that the concentration of the glutamate in the perilymph increased dramatically after transient ischemia[5]. In addition, the threshold of the compound action potential was 30 dB higher than before the ischemic state. Jäger et al. demonstrated using microdialysis that the concentration of the glutamate and aspartate in perilymph increased after acute noise trauma[6]. All of these studies showed that excess glutamate in the perilymph causes hearing loss and changes in the structure of the cochlea. The mechanism of excitotoxicity is believed to be due to large cation influxes and a passive entry of Cl-, and water that gives rise to acute swelling of the dendrites[7]. Figure 1 shows schematic drawing illustrating the consequence of excitotoxicity at the level of the inner hair cell. Prolonged stimulation results in an excessive release of glutamate. An increased uptake of calcium and water results in swelling of the afferent dendrites.

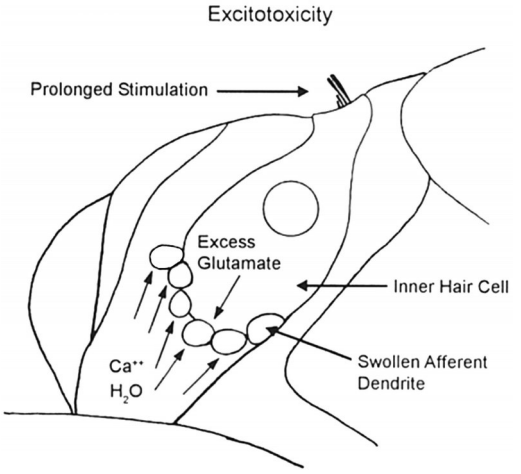

Fig.1 Schematic drawing illustrating the consequence of excitotoxicity at the level of the inner hair cell. Prolonged stimulation results in an excessive release of glumate. An increased uptake of calcium and water results in swelling of the afferent dendrites.

Corresponding author: DUAN Maoli, M.D, PhD, Department of Clinical Sciences, Intervention, Department of Audiology, Department of Clinical Neuroscience, Department of Otolaryngology Head and Neck, Karolinska University Hospital, Stockholm, 171 76 Stockholm, Sweden
E mail: maoli.duan@ki.se

In addition, I summarise the common path of noise trauma and aminoglycosides damage (figure 2).

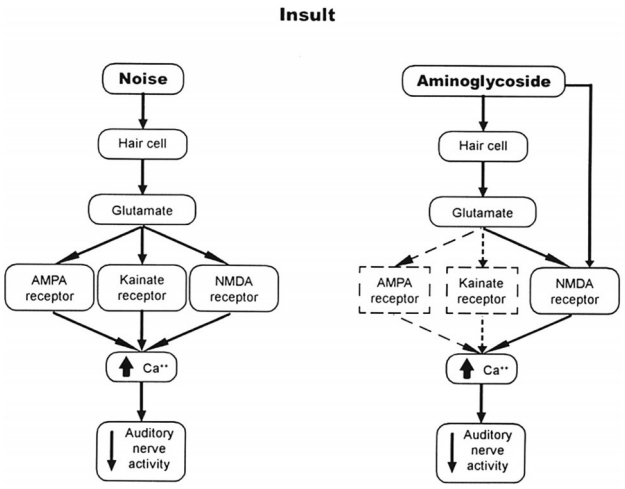

Fig.2 Summary diagrams illustrating the sites of cochlear injury induced by noise and aminoglycosides. Solid lines illustrate the affected sites while the dashed lines indicate unaffected sites.

Protective role of glutamate receptor antagonists

Neuroprotection by the glutamate receptor antagonist has been widely investigated. Pingle et al. demonstrated that neuronal death of CA1 pyramidal cells in vitro following either hypoxia or ischemia was prevented by pre-incubation with the non-NMDA receptor antagonist, CNQX and the NMDA receptor antagonist, MK 801 [8]. In addition, MK 801 or CNQX also prevented pyramidal cell death induced by either hypoxia or ischemia if added immediately post-insult. Many investigators have found that glutamate receptor antagonists have a neuroprotective role when administrated in vivo. Solberg et al found that photoreceptor-cell loss to argon laser lesions was significantly less using MK 801 than in control animals[9]. Gill et al. demonstrated that MK 801 significantly reduced ischemic brain damage induced by middle cerebral artery occlusion compared to saline-treated animals [10]. Interestingly bFGF enhances the protective effects of MK 801 against ischemic neuronal injury in vitro [11]. In the auditory peripheral system, a protective role by the glutamate receptor antagonist has been investigated. The excitotoxicity can be prevented by a non-NMDA receptor antagonist [4]. In addition, they found that AMPA-induced swelling of the dendrites under the inner hair cells could be partly prevented by the non-NMDA receptor antagonist DNQX, while the combination of a NMDA receptor antagonist and non-NMDA receptor antagonist could completely prevent the swelling of the dendrites. Janssen R. demonstrated that glutamate could lead to high frequencies hearing loss which was prevented by the glutamate receptor antagonist kynuretic acid or the NMDA receptor antagonist MK 801 [12]. Noise-induced swelling of the dendrites under the inner hair cells has been found to be prevented by MK 801 and kynuretic acid[13, 14].

Neurotrophic factors

Nerve growth factor (NGF), a prototype neurotrophic factor was discovered more than 40 years ago by Levi-Montalcini, for which work she received the Nobel Prize in Physiology or Medicine in 1986. NGF has been shown to promote growth, survival and differentiation of neurons. More recently, other similar factors and their receptors have been characterized. Members of the neurotrophin family which have been identified include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin3 (NT-3), neurotrophin-4/5 (NT4/5), and glial cell line-derived neurotrophic factor (GDNF). All of these neurotrophins effects (cell survival and differentiation) are caused by a set of high affinity receptor tyrosine kinases. NGF binds TrkA, BDNF and NT4/5 bind TrkB, NT- 3 is more preferential to TrkC, and GDNF binds GDNF-receptor alpha (GDNFR-alpha). There are other factors like ciliary neurotrophic factor (CNTF), members of the fibroblast growth factor (FGF) family, insulin-like growth factor I (IGF-1) etc. which have been characterized very recently. There is increasing evidence that neurotrophins are involved in processes of neuronal plasticity [15]. The activity-dependent regulation of neurotrophin synthesis by classical neurotransmitters in the central nervous system has been demonstrated. Up-regulation is affected by glutamate (NMDA and non-NMDA receptor) and also acetylcholine whereas down-regulation is mediated predominantly by GABA. The mRNA for NT-3, BDNF and their receptor trk B and Trk C are expressed in the inner ear sensory epithelia and the cochlear and vestibular ganglia [16]. The amount of BDNF mRNA are low in early neonatal stages in both cochlear and vestibular sensory epithelia [17]. NT-3 mRNA is expressed ini-