*Neuroscience* 285 (2015) 248–259

# NEUROSCIENCE FOREFRONT REVIEW

# FROM DEVELOPMENT TO DISEASE: DIVERSE FUNCTIONS OF NMDA-TYPE GLUTAMATE RECEPTORS IN THE LOWER AUDITORY PATHWAY

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**Abstract—N-methyl-D-aspartate receptors (NMDA-Rs) are located at each synapse in the lower auditory pathway of mammals and avians. Characterized by a slow and long-lasting excitatory response upon glutamate activation, their existence in a sensory system biologically engineered for speed and precision seems counterintuitive. In this review we consider the diverse functions of NMDA-Rs. Their developmental regulation and unique subunit composition in the inner ear promote protective and neurotrophic roles following acute insult by regulating AMPA-R expression and assisting in the restoration of synaptic inputs. This contrasts with chronic damage where overactivation of NMDA-Rs is implicated in neuronal death. These functions are thought to be involved in auditory diseases, including noise-induced hearing loss, neural presbycusis, and tinnitus via aberrant excitation. A more traditional role emerges in the developing auditory brainstem, where NMDA-Rs are downregulated and switch subunit composition with maturation. Their biophysical properties also contribute to synaptic dynamics resembling long-term plasticity. At mature synapses they support reliable auditory processing by increasing the probability of action potential generation, regulating first-spike latency, and maintaining reliable action potential firing. Thus, NMDA-R functions in the lower auditory pathway are diverse, contributing to synaptic development, plasticity, temporal processing, and diseases.**

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*Abbreviations:* AMPA-R, α-amino-3-hydroxy-4-isoxazolepropionic acid-type glutamate receptor; DCN, dorsal cochlear nucleus; DNLL, dorsal nucleus of the lateral lemniscus; GABA, γ-aminobutyric acid; ICX, external nucleus of the inferior colliculus; IHC, inner hair cell; LSO, lateral superior olive; LTD, long-term depression; LTP, long-term potentiation; mGluR, metabotropic glutamate receptors; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; NL, nucleus laminaris; NM, nucleus magnocellularis; NMDA-R, N-methyl-D-aspartate receptor; SGN, spiral ganglion neuron; VCN, ventral cochlear nucleus.

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**Key words: auditory development, auditory disease, glutamate, hearing, N-methyl-D-aspartate receptors.**

Contents



## INTRODUCTION

Glutamate is the primary excitatory neurotransmitter in the brain, including the auditory system of mammals and avians. When released from presynaptic terminals, it binds to postsynaptic AMPA- and N-methyl-D-aspartate-receptors (AMPA-Rs and NMDA-Rs, respectively). The fast and temporally precise encoding of sound is heavily dependent on synaptic AMPA-Rs (Trussell, 1998; Parks, 2000). NMDA-R responses however, are slower and longer lasting than AMPA-Rs and although NMDA-Rs' presence suggests a functional role in hearing, their properties do not appear beneficial to a system designed for speed and reliability. In this review, we consider the role of NMDA-Rs in the auditory system by following the ascending pathway from the inner ear to the midbrain

http://dx.doi.org/10.1016/j.neuroscience.2014.11.027
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(Fig. 1). We highlight NMDA-Rs' diverse role in auditory synaptic development, plasticity, and temporal processing, and discuss their contribution to auditory diseases, including noise-induced hearing loss, neural presbycusis, and peripheral tinnitus.

## NMDA-RS IN THE LOWER AUDITORY PATHWAY OF MAMMALS AND AVIANS

NMDA-Rs are ligand-gated and voltage-dependent cation channels permeable to sodium, potassium, and calcium ions. They are activated by glutamate and the co-agonist glycine. At negative membrane potentials NMDA-Rs are blocked by extracellular magnesium, requiring AMPA-R depolarization to relieve this block. NMDA-R composition includes the mandatory GluN1 subunit and a variety of GluN2A, B, C, and D subunits. NMDA-Rs containing GluN2A are characterized by fast response kinetics (lasting tens of milliseconds), while NMDA-Rs containing GluN2B are characterized by slow response kinetics (lasting hundreds of milliseconds). The GluN2B subunit usually dominates at auditory synapses during early development while more mature synapses contain the GluN2A subunit. All of these features however, are not always shared in the lower auditory pathway, providing a unique platform to examine diverse NMDA-R functions as they relate to hearing. Readers interested in general NMDA-R function elsewhere in the brain are referred to the following reviews (Traynelis et al., 2010; Luscher and Malenka, 2012; Bartlett and Wang, 2013; Paoletti et al., 2013; Sanz-Clemente et al., 2013).

### Mammalian inner hair cell-spiral ganglion neuron (IHC-SGN) synapse

Sound is transmitted to the central auditory system in the form of action potentials via the auditory nerve. Type I SGNs make up ~90% of nerve fibers and their dendrites exclusively contact the base of IHCs in the cochlea. At the mammalian IHC-SGN synapse, NMDA-Rs are present in early auditory development and studies show a transient expression of GluN1 and GluN2A subunits (Knipper et al., 1997). With maturation, there is a strong reduction in GluN1 expression, a complete elimination of GluN2A (Knipper et al., 1997; Ruel et al., 2008), and an increase in GluN2B, C and D subunits (Puel, 1995; Ruel et al., 2008). This is opposite from other developing auditory nuclei where GluN2B is downregulated and GluN2A is upregulated.

As such, NMDA-Rs are not directly involved in glutamatergic transmission at IHC-SGN synapses (Puel et al., 1991, 2002; Ruel et al., 1999). Physiological recordings show a lack of NMDA-R responses, despite removal of magnesium blockade and application of the co-agonist glycine (Glowatzki and Fuchs, 2002). Instead, NMDA-Rs are thought to contribute to the regulation of surface AMPA-R expression, since Chen et al. (2007) found a decrease in expression of surface AMPA-Rs upon application of an NMDA-R agonist. This decrease in AMPA-R expression was blocked by the application of NMDA-

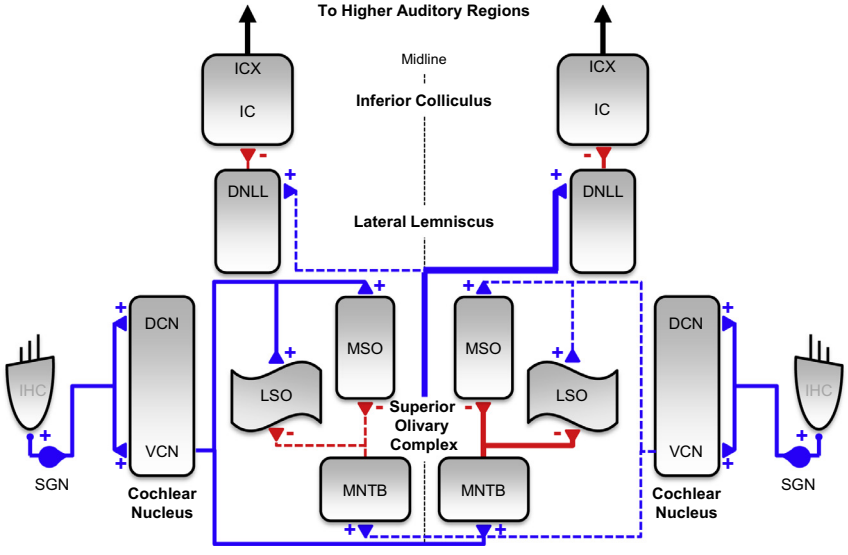


**Fig. 1.** Schematic representation of the mammalian lower auditory pathway. Sound is converted into electrical activity by inner hair cells (IHC) of the cochlea. Neural action potentials are generated by spiral ganglion neurons (SGN) of the vestibulocochlear cranial nerve VIII. Action potential activity is sent along the ascending central auditory pathway that includes the cochlear nucleus (CN) and superior olivary complex (SOC) located in the lower pons, the lateral lemniscus (LL) located in the brainstem, and the inferior colliculus (IC) located in the midbrain. Processed information is then sent to higher auditory regions including the medial geniculate body (located in the thalamus) and the auditory cortex (not shown). The CN contains the ventral and dorsal cochlear nuclei (VCN and DCN, respectively). The SOC contains the lateral superior olive, medial superior olive, and medial nucleus of the trapezoid body (LSO, MSO, and MNTB, respectively). Specific subregions of the superior olivary complex are omitted for clarity. The lateral lemniscus contains several nuclei but of interest for this review is the dorsal nucleus (DNLL). The IC contains the external nucleus (ICX, most prominent in avians). Blue lines and plus symbols indicate excitatory pathway. Red lines and minus symbols represents inhibitory pathways. Dashed lines are used to clarify binaural pathways. For comparison, a portion of the mammalian VCN and MSO are analogous in structure and function to the avian nucleus magnocellularis (NM) and nucleus laminaris (NL), respectively.

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