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Glutamate Excitotoxicity and Ischemic Reperfusion Injury in Spiral Ganglion Neurons During Hearing Loss

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"This literature review offers a thorough molecular synthesis of how pathological glutamate accumulation is triggered by ischemic hypoxia and subsequent reperfusion, driving calcium-mediated calpain activation, mitochondrial collapse, and apoptosis-inducing factor translocation in spiral ganglion neurons during sensorineural hearing loss."

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Abstract

Neurosensory hearing loss in mammals is a common disorder caused by the progressive loss of sensory hair cells and spiral ganglion neurons (SGNs) in the cochlea. Genetic defects and mechanical acoustic trauma have been clinically recognized throughout, but profound metabolic insults and vascular compromise can also lead to both acute and progressive loss of hearing capability. Spiral ganglion neurons (the vast majority of which constitute the type I afferents that convey the primary auditory signal from the inner hair cells to the central auditory pathway) are particularly susceptible to oxygen and energy deprivation. During cochlear ischemia and hypoxia, rapid depletion of adenosine triphosphate causes a dramatic collapse of neuronal transmembrane potentials and failure of the surrounding glial glutamate uptake machinery, particularly the glutamate aspartate transporter (GLAST). Disruption of this homeostatic balance leads to uncontrolled aggregates of synaptic glutamate in the afferent synapse that culminate in deluges of glutamate excitotoxicity. Non-N-methyl-D-aspartate (non-NMDA) ionotropic receptor hyperactivation (most commonly calcium-permeable GluA2-lacking AMPA receptors) releases extracellular calcium into auditory nerve terminals and neuronal somas. This surge in calcium overwhelms buffering and activates cytotoxic calpain pathways, destabilizes mitochondrial membranes, drives caspase-independent nuclear translocation of apoptosis-inducing factor (AIF), and precipitates disintegration of the neuron cell. During reperfusion, this injury is exacerbated by free radical storms and excess nitric oxide. This review of literature summarizes the pathophysiological mechanisms of ischemic excitotoxicity in auditory neurons and discusses emerging otoprotective interventions to protect auditory nerve integrity.

Keywords: Glutamate excitotoxicity, Ischemia reperfusion injury, Spiral ganglion neurons, Sensorineural hearing loss, Calcium overload, Calpain activation, Apoptosis inducing factor, AMPA receptor

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Introduction

In mammals, encoding of complex sounds also begins in the cochlea, which relies on an accurate conversion of acoustic vibrations into temporally precise bioelectric signals. This sensory transduction is facilitated by the first-order auditory afferent fibers, the spiral ganglion neurons (SGNs). Type I spiral ganglion neurons of the auditory system typically make up ~90-95% of the ganglion pool. A type I neuron contacts a single inner hair cell (IHC) via a specialized ribbon synapse and an unbranched peripheral dendrite and sends a central axon through the modiolus to the cochlear nuclei in the brainstem. The auditory ribbon synapse uses almost exclusively glutamate, with rapid discharge of free transmitter L-glutamate. The inner hair cells are glutamatergic and release glutamate from specialized small synaptic vesicles by the action of a vesicular glutamate transporter subtype (VGLUT3) at presynaptic active zones onto dense patches of postsynaptic receptor at the tip of the auditory nerve fiber's dendritic bouton(Ding et al., 2015; Hu, Rutherford, & Green, 2020).

Glutamate is normally tightly regulated at the synapse because excess extracellular accumulation is neurotoxic and limits temporal acuity. However, this ionic homeostasis and synaptic cycling come with a voracious metabolic demand, and the cochlea is highly sensitive to ischemia. For example, if vasospasm or vascular thrombosis suddenly halts the microcirculation of the labyrinth, or if the cochlea is overstimulated or the systemic circulation fails and cuts off the blood supplied by the bone, an abrupt but devastating ischemia and hypoxia will overwhelm the sensory and neural elements in the labyrinth(Kitama et al., 2025; Polikarpov, Smolyarchuk, Fisenko, & Bakaeva, 2026; Tabuchi et al., 2010).

The dense capillary bed of the lateral cochlear wall, the heart of metabolic power as noted in our earlier review of strial vascular degeneration and collapse of the endocochlear potential, provides the bioelectric driving forces that power hearing and decays rapidly when microvascular perfusion is diminished. Based on this simple premise, cellular ischemia rapidly destroys the neural component of the inner ear(Meuser et al., 2026). Eventually, nerve endings and other supporting cells are simply starved of energy, glucose, and oxygen when they do not have adenosine triphosphate (ATP) in their sole possession, which is hardly conducive to preventing this pathology(Tabuchi et al., 2010; Wang & Puel, 2018; K. Xu et al., 2023). In metabolic and bioenergetic terms, the postmitotic neuroepithelia of the inner ear sensory systems lack the protectively buffered organ systems, leaving them prey to rampant bioenergetic depletion and exacerbating the bioenergetic disaster foreshadowed with mitochondrially derived ROS cascades. Similarly, in post-ischemic conditions, the spiral ganglion synapse is left with excess extracellular glutamate that cannot be cleared from the tight synaptic cleft(Meuser et al., 2026). This prolonged extracellular accumulation of glutamate leads to calamitous glutamate excitotoxicity. The postsynaptic receptors are saturated, allowing divalent cations and water to enter massively into the dendrites to be swollen and inflict damage on organelles of the cell, resulting in a more delayed death(Askew et al., 2015; Polikarpov et al., 2026) , unlike a temporary action potential. The elucidation of the molecular mechanism of glutamate excitotoxicity in ischemic reperfusion injury of spiral ganglion neurons is central to the pathophysiology of sudden sensorineural hearing loss, noise-induced synaptopathy, and hidden hearing loss(Pasdelou et al., 2024; Tabuchi et al., 2010). In this paper, we review the present biophysics, enzymology, and oxidative cascades of ischemic- and auditory neuropathy from the swelling of synaptic substructures to the terminal death of neurons.

1. Ischemia of the cochlea and bioenergetic failure of its afferent innervation

As the mammalian inner ear is an end-artery organ and cochlear perfusion depends

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on terminal branches of the labyrinthine artery with little collateral circulation, the inner ear is uniquely vulnerable to vascular injury(Peng et al., 2004). As cochlear blood flow decreases, the partial pressure of oxygen in cochlear tissue falls within seconds, and oxidative phosphorylation by the mitochondrial electron transport chain ceases. Sustenance of energy production by oxidative metabolism dependent on oxygen requires a continuous substrate supply to neurons, and the intracellular pool is swiftly depleted when ischemia is present(Bing et al., 2015; Tabuchi et al., 2010).

ATP depletion predictably results in failure of energy-dependent active transports, most notably the ubiquitous sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pump. Under normal physiological parameters, this pump uses a significant proportion of cellular energy to pump sodium out in exchange for potassium, maintaining a steep negative resting membrane potential necessary for excitability. If ATP levels fall below critical values, active ionic extrusion stops, and sodium and chloride leak through the plasma membrane down electrochemical gradients. This "osmotically obliged" water seems to account for the dramatic cytotoxic edema and results in immediate type I afferent terminal ballooning (the ultrastructural correlate of cytotoxic edema) immediately beneath inner hair cells(Bing et al., 2015; Tang et al., 2014).

Studies on animal models of reversible cochlear ischemia provided evidence to suggest that dendrites of the auditory nerves are the most ischemia-sensitive cell type throughout the whole inner ear. Already after five minutes of blood flow interruption, swollen afferent terminals can be observed in the absence of structural changes in inner or outer sensory hair cells. If the ischemic period extends beyond 10-15 minutes, irreversible structural injury takes place, culminating in the complete detachment of synaptic boutons, bleb formation, nuclear pyknosis, and disintegration of the organ of Corti(Altun et al., 2014; K. Xu et al., 2023).

2. Molecular mechanisms of synaptic glutamate accumulation and transporter failure

Indeed, free accumulation of glutamate in the sub-inner hair cell synaptic space is the key factor that plays an essential role in the path bridging ischemia and neurodegenerative modification of spiral ganglion cells. In the resting state, free glutamate in the synaptic cleft extracellular space is maintained in the micromolar range to allow temporal resolution without depolarization of the postsynaptic membrane. Termination of glutamatergic neurotransmission is not achieved by enzymatic degradation in the extracellular space but rather by rapid clearance via highly selective, sodium-dependent excitatory amino acid transporters(Saidia et al., 2024; Seidman & Quirk, 1991).

In the cochlea, the major glutamate transporter for synaptic clearance is glutamate aspartate transporter (GLAST; EAAT1). Immunohistochemical studies have demonstrated that GLAST is highly expressed on the plasma membrane of supporting cells in contact with inner hair cells (inner phalangeal cells and inner border cells) and on the membrane of spiral ganglion neuronal somata surrounded by satellite glial cells(Peng et al., 2004). GLAST moves glutamate into the cell along with sodium and hydrogen ions (co-transport down their electrochemical gradient) and a potassium ion (counter-transport). Once inside supporting cells, glutamate is converted to biologically inert glutamine via glutamine synthase, which is subsequently fed back to hair cells, completing the glutamate-glutamine cycle(Usami, Takumi, Matsubara, Fujita, & Ottersen, 2001).

This uptake mechanism is doubly jeopardized by ischemia. First, the absence of oxygen and glucose rapidly depolarizes presynaptic inner hair cells, opening voltage dependent calcium channels and triggering nonselective release from caged vesicles of glutamate into the synaptic cleft. Second, the dissipation of the transmembrane sodium

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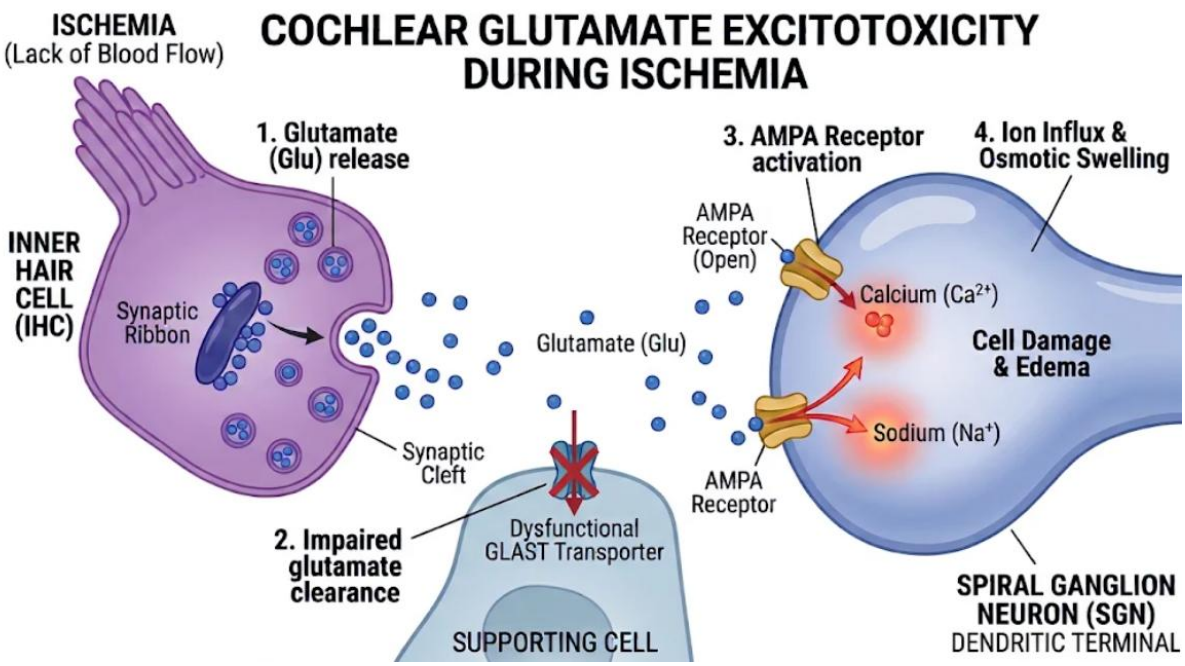

Figure 1. Excitotoxicity of glutamate at the cochlear inner hair cell-spiral ganglion neuron synapse during ischemia. Ischemia results in excessive glutamate release from the IHC (1) and impaired glutamate clearance by the dysfunctional GLAST in the supporting cell (2), which excites the AMPA receptors at the SGN dendritic terminal (3). This influx of Ca^{2+} and Na^{+} sequesters water into the cell, resulting in osmotic swelling and edema, which then leads to cell damage (4).

gradient potentiates GLAST and reverses glutamate flow. With the inward sodium gradient no longer driving movement, the transporter becomes an efflux pathway, moving glutamate out of the supporting cells into the extracellular space. This mechanism is validated by the GLAST genotype deletion studies, in which such mice show severe exacerbation of noise- and ischemia-induced synaptopathy, implying that the active transporter function is necessary to protect the auditory dendrites from excitotoxic insult(Hu et al., 2020; Meuser et al., 2026; Tabuchi et al., 2010). The postsynaptic dendritic bouton of the type I spiral ganglion neuron, the inner hair cell, and the surrounding supporting cells are structurally juxtaposed in **Figure 1** to demonstrate how ischemic energy depletion transforms a precisely calibrated communication node into a site of localized neurotoxicity. Maintained millimolar levels of glutamate stimulate all surrounding ionotropic receptors on this unmyelinated dendritic terminal(Hu et al., 2020).

3. Overactivation of Postsynaptic Receptor and Calcium Influx

NMDA Receptors and Ionotropic Glutamate Receptor Channels; AMPA, Kainate Family in Mammalian Spiral Ganglion. While NMDA receptor overactivation is the primary excitotoxic pathway in the CNS, increasing pharmacologic and physiologic literature indicates that excitotoxic injury in the cochlea is independent of the NMDA receptor profile(Hu et al., 2020; Polikarpov et al., 2026). NMDA receptor antagonists (MK-801 and APV) applied topically or systemically provide little to no protection against dendritic swelling or ischemic threshold cochlear potential in animal models. Conversely, competitive or noncompetitive non-NMDA receptor blockers (DNQX or GYKI 53784) fully protect against acute excitotoxic swelling and

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preserve compound action potentials. This reinforces the notion that AMPA and kainate receptor subtypes are the main executioners of auditory excitotoxicity(Diuba et al., 2025).

AMPA receptors are heterotetramers of four subunits (GluA1-4). Of the four subunits, only the edited (post-transcriptional) form of GluA2 produces an AMPA receptor channel that is impermeable to divalent cations such as calcium and zinc ions. AMPA receptors containing the edited GluA2 subunit are impermeable to divalent cations and permeable only to sodium and potassium ions. Tetramers of AMPA receptors lacking GluA2 are very permeable to calcium ions and have much larger single-channel conductances(Hu et al., 2020; Polikarpov et al., 2026).

Electrophysiological and high-resolution confocal imaging studies have demonstrated that GluA2 is present at the adult auditory synapse, but not evenly distributed in the postsynaptic density. Calcium-permeable AMPARs (CP-AMPARs) that lack GluA2 are inserted into subcompartments of the dendritic membrane known as nanodomains. Prolonged exposure to ischemic glutamate allows these CP-AMPAR complexes to permit a massive influx of extracellular calcium into the dendritic cytoplasm. Selective blockers of GluA2-lacking AMPA receptors (e.g., selective dicationic adamantane derivative IEM-1460) confer robust histological and functional protection against synaptic disintegration ensuing excitotoxic damage(Hu et al., 2020; Polikarpov et al., 2026).

Besides the above AMPA receptors, tissue acidosis accompanying ischemia facilitates cation influx. Protons and lactic acid build up, activating acid-sensing ion channels, notably ASIC2, which is highly expressed on spiral ganglion neurons. Proton gating of ASIC2 channels can cause permanent inward depolarizing currents, which further enhance calcium influx via voltage-dependent channels, adding to the ionic disruption intracellularly(Peng et al., 2004).

4. Downstream Degradation Pathways: Calpain Activation, Mitochondrial Collapse, and Apoptosis Inducing Factor

Ca^{2+} Accumulation in the Nuclei of Spiral Ganglion Neurons and Proteolytic/Metabolic Degradation Cascades Due to the small volume of the unmyelinated dendritic bouton, rapid calcium influx rapidly saturates endogenous calcium-binding proteins (e.g., parvalbumin, calbindin), activating calcium-dependent intracellular enzymes(Ding et al., 2015; Kitama et al., 2025).

The first of the destructive enzymes are calpains, a group of nonlysosomal neutral cysteine proteases, which are expressed along spiral ganglion. Calpains exist as inactive cytosolic entities under basal conditions but are autocleaved and membrane-bound in response to modest increases in calcium concentrations (i.e., micromolar levels). Super-activated calpains cleave α-fodrin, neurofilaments, and microtubule-associated proteins, thereby compromising the structural integrity of the auditory dendrite. Additionally, the activation of calpains leads to the cleavage and inactivation of PMCA (plasma membrane calcium ATPase), which results in the neuron losing its last internal mechanism for expelling its excessive calcium load across its membrane into the external medium(Ding et al., 2015).

Excess calcium loading is sequestered in local mitochondria through the mitochondrial calcium uniporter. Mild calcium uptake dampens minor physiological disturbances, whereas massive calcium overload ruptures the mitochondrial transmembrane potential. Excess calcium subsequently opens the mitochondrial permeability transition pore, producing osmotic swelling of the mitochondrial matrix, focal destruction of the cristae, and rupture of the mitochondrial outer membrane(Ding et al., 2015; Wang & Puel, 2018).

Transmission electron microscopy of these glutamate-damaged spiral ganglion neurons reveals diffuse mitochondrial degeneration, dense cytoplasmic vacuoles,

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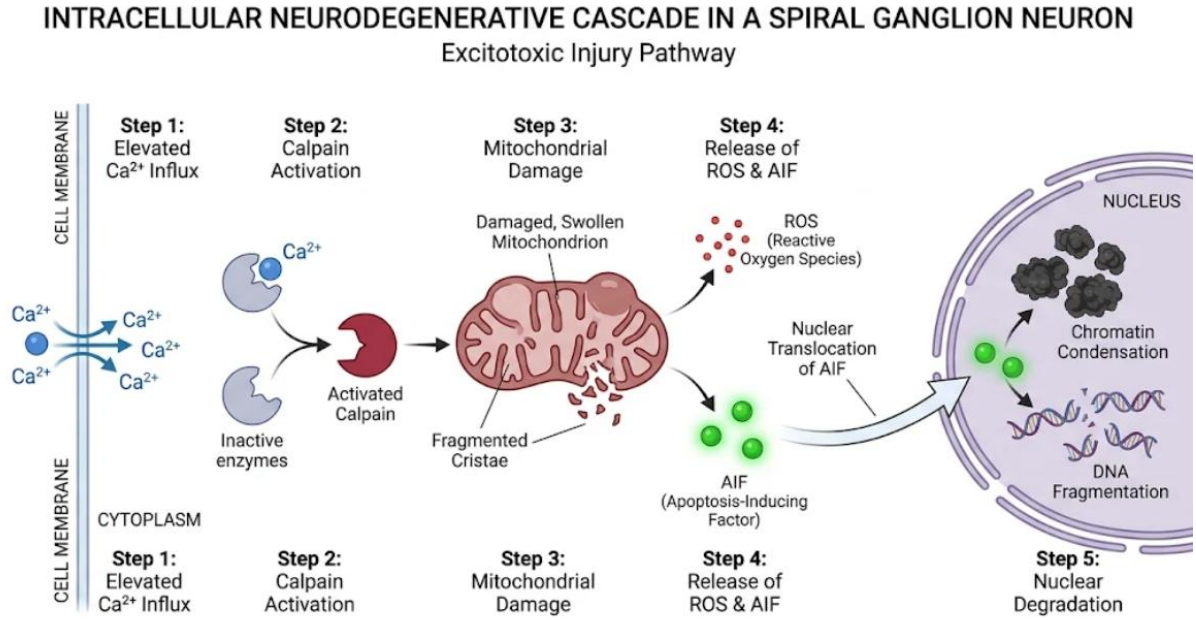

Figure 2. Excitotoxic neurodegeneration of spiral ganglion neurons. Increased Ca^{2+} influx and swelling of mitochondria with fragmentation of cristae and activation of calpain to release ROS and apoptosis-inducing factor (AIF) to the nucleus to condense the chromatin and fragment the DNA.

and dilated endoplasmic reticulum. Of special interest, biochemical and molecular results suggest that the apoptotic death of the spiral ganglion neurons triggered by glutamate excitotoxicity differs from classic caspase-associated apoptosis. Specifically, vigorous glutamate perfusion does not modify (or attenuates) activation of caspase-3 but, instead, robustly activates apoptosis-inducing factor (AIF)(Ding et al., 2015).

AIF is a mitochondrial flavoprotein and is usually an oxidoreductase in the respiratory electron transport chain. Exogenous calcium activates mitochondrial mu-calpain, which cleaves membrane-bound AIF to its soluble truncated form. The truncated AIF translocates to the nucleus of the spiral ganglion neuron from the ruptured mitochondrial membranes in association with the importins and cyclophilin A. Once in the nucleus, AIF binds to chromatin, inducing extensive peripheral chromatin condensation and massive DNA fragmentation as high molecular weight DNA fragments. The synthetic calpain inhibitors (MDL-28170 and PD 150606) block calpain cleavage, AIF nuclear translocation, and excitotoxic spiral ganglion apoptosis(Ding et al., 2015; Kitama et al., 2025; Wang & Puel, 2018).

The degenerative cascade, therefore, forms a biological cascade where glutamate overactivation leads to calcium influx through CP-AMPARs, resulting in calpain activation and finally triggering mitochondrial permeability transition AIF entry into the nucleus and irreversible breakdown of spiral ganglion nuclei chromatin (**Figure 2**).

5. Secondary Burst of Free Radicals in Ischemic Reperfusion

Excitotoxic and ROS/RNS-Induced Cochlear Injury From Reperfusion of the Cochlear Blood Flow: The initial pathophysiologic insult to cochlear tissue is the lack of oxygen and glucose; the reperfusion of the cochlear flow is a second injury mediated by ROS/RNS. The introduction of molecular oxygen into the microenvironment of the injured tissue provokes a vigorous period of oxidative and nitrosative stress(Kitama et al., 2025; Tabuchi et al., 2010; K. Xu et al., 2023).

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Multiple enzymatic and non-enzymatic sources contribute to the reperfusion burst in the inner ear:

1. **Mitochondrial electron leakage:** Ischemic damage to complexes I, III, and IV of the respiratory chain in the mitochondria prevents electron flow down the chain. Leaked electrons reoxygenate and directly reduce molecular oxygen, generating copious amounts of superoxide anions(Kitama et al., 2025).
2. **Activation of xanthine oxidase:** Hypoxanthine accumulated inside cells from hypoxic catabolism of cellular ATP; Meanwhile, calpain converts xanthine dehydrogenase into xanthine oxidase. When oxygen returns during reperfusion, the hypoxanthine formed is converted by xanthine oxidase into uric acid, producing bursts of superoxide anion and H_2O_2(Tabuchi et al., 2010).
3. **Uncoupling of nitric oxide synthase:** Endothelial nitric oxide synthase (eNOS) generates physiologic nitric oxide for the adjustment of vascular diameter; however, eNOS uncoupling occurs due to oxidation of tetrahydrobiopterin, the cofactor needed for eNOS activity. This leads to eNOS enzymatically producing superoxide instead of nitric oxide(Kitama et al., 2025).
4. **Inducible nitric oxide synthase:** nNOS generates nitric oxide in the initial phase, and iNOS in delayed nitric oxide release; reperfusion also augments these. Superoxide reacts at diffusion-controlled rates and, together with the excess of nitric oxide, may form peroxynitrite ($ONOO^-$), a highly reactive and destructive nitrogen derivative(Kitama et al., 2025; Tabuchi et al., 2010).

Hydroxyl radicals generated by peroxynitrite and the iron Fenton reaction indiscriminately attack polyunsaturated fatty acids in membranous organelles and neurons, producing widespread lipid peroxidation. This peroxidation yields cytotoxic reactive aldehydes (namely, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)), which covalently cross-link and deregulate membrane protein actions and disrupt membrane fluidity. In fact, the increased amounts of MDA and 4-HNE in cochlear tissue in the glutamic excitotoxic action reproduce the features of oxidative cellular stress characteristic of severe acoustic trauma and ischemic insult(Saidia et al., 2024; Tabuchi et al., 2010; Wang & Puel, 2018).

Discussion

The intricate understanding of the mechanism of glutamate excitotoxicity and ischemic reperfusion cascades has revolutionized the concept of acquired sensorineural hearing loss. Sensorineural hearing loss was previously viewed as a destructive process of sensory hair cells. However, with the recognition of auditory synaptopathy and primary neuropathy as primary pathophysiological events (as acute excitotoxic loss of ribbon synapses and spiral ganglion dendrites, often in the absence of loss of hair cell bodies), new nomenclature of cochlear excitotoxicity is emerging(Diuba et al., 2025; Hu et al., 2020).

The most intriguing aspect of cochlear excitotoxicity may be the notion of functional recovery dissociated from a permanent synaptopathy. In animal models of acute excitotoxic injury, auditory nerve compound action potential (CAP) recordings show substantial recovery of threshold and amplitude over the following weeks. In single-fiber electrophysiology studies, this recovery is in some cases associated with homeostatic phenotypic changes in the surviving auditory nerve fibers(Diuba et al., 2025). So somehow, by functional reinnervation and hyperactivity of individual fiber responses in the pairing of properties, a new pool of low-spontaneous fibers (which

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often seem indistinguishable from high-spontaneous fibers) is generated, able to fire in the presence of sound and possibly with increased synchrony, as compensation for the inevitable loss of more than half of the original synapses. However, such an adaptive hyperresponsivity, when occurring at a higher level than in the peripheral auditory nerve, may run amok and become maladaptive, producing pathological neuronal hyperactivity in central auditory brainstem and central auditory cortex in tinnitus and hyperacusis(W. Xu et al., 2026).

Subsequent stages of the excitotoxic cascade may provide opportunities for phased pharmacological intervention:

- **Receptor-Targeted Antagonists:** The design of selective inhibitors of calcium-permeable AMPA receptors (e.g., IEM-1460) offers a promising strategy to prevent excitotoxic synaptopathy without disrupting basal excitatory neurotransmission(Hu et al., 2020).
- **Calpain and Apoptotic Inhibitors:** Blockade of downstream Ca^{2+}-incriminated elements using cell-permeable calpain inhibitors (including MDL-28170) or an AIF (apoptosis-inducing factor) inactivator attenuates neurotoxicity and prevents structural lysis from excitotoxic damage(Ding et al., 2015).
- **Free Radical Scavengers:** Supplementation with antioxidants (e.g., resveratrol, ebselen, N-acetylcysteine) can neutralize free radicals during the crucial early reperfusion period (peak MDA formation and lipid peroxidation) and enhance neuronal survival(K. Xu et al., 2023).
- **Neurotrophic Support:** BDNF, NT-3, or novel small-molecule TrkB agonists (LM22A-4 and CF3CN) induce robust systemic neuritogenesis, enhance functional ribbon synapses with inner hair cells, and mitigate the postexcitotoxic free radical fallout(Saidia et al., 2024).

These pre-clinical observations are encouraging but face considerable physiological hurdles to translation into human clinical practice. Systemically administered pharmacologic agents typically poorly bathe the inner ear via the blood-labyrinth barrier and rarely achieve concentrations within intracochlear fluid compartments that are therapeutically beneficial. Clinical progress in the future may therefore depend on local drug-infusion techniques (magnetic nanoparticles and/or round-window-drug-delivery penetrating technologies) that allow drugs to be maintained at clinically relevant concentrations in inner ear perilymph, with tolerable side effects, for a sufficient time to have therapeutic benefit(Duan, Peng, & Wang, 2024; Kitama et al., 2025).

Conclusion

Two interconnected pathological cascades during sensorineural hearing loss, ischemic reperfusion injury and glutamate excitotoxicity, compromise the functions and survival of spiral ganglion neurons. With ischemic conditions, metabolic re-synthesis of energy cannot be maintained, with normal active transport of ion and the glial re-uptake of glutamate over-replenishing the auditory ribbon synapse with toxic transmitter concentration. This overactivates calcium-permeable AMPA receptors inducing toxic divalent cation entry and activation of calpain proteases, mitochondrial rupture, and nuclear translocation of the apoptosis-inducing factor in a caspase-independent manner. Reperfusion compounds this injury by triggering oxidative lipid peroxidation and peroxynitrite formation. Exciting new possibilities for the prevention of neurosensory degeneration to save human hearing arise from the blockade of calcium permeable receptors, a calpain suppressor, antioxidant scavengers, and neurotrophic support that interrupts this destructive cascade.

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