Neuroscience of Tinnitus

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KEYWORDS

• Tinnitus • Neural networks • Excitotoxicity • Plasticity • Glutamic acid • NMDA • AMPA

KEY POINTS

- Tinnitus is the result of changes in a distributed central neural network following cochlear insult.
- The pathologic conditions producing tinnitus seem to differ at different network levels.
- Understanding and therapeutically addressing tinnitus is complicated by its heterogeneous and distributed pathophysiology.
- Functional brain imaging, histocytochemical analysis, and laboratory and clinical studies have contributed to the current understanding.
- Current and emergent treatment options are targeting pathologic functions revealed by this research.

Tinnitus is the most common chronic auditory disorder. National Health and Nutrition Examination Survey data estimate that approximately 45 million American adults experience tinnitus and 15 million report frequent symptoms.[1–5] Although the definition of tinnitus may affect survey figures, adult prevalence is between 6% and 19%.[6] Hearing loss is the greatest risk factor for developing tinnitus and risk increases with a history of high-level sound exposure earlier in life.[7] The popularity of in-ear and headphone speakers used with recreational sound devices, in addition to the increased average age of the population, and associated cumulative noise exposure, predict a growing health concern.[4,5,8–10] In addition, the US Department of Veterans Affairs estimated that in 2014 approximately 22 million Americans had served in the military,[11] an environment that exposes young adults to potentially damaging high-level sound that places them at increased risk of tinnitus.[12]

Despite the great number people with symptoms, only approximately one-third of those with tinnitus seek care because of its bothersome effects (eg, changes in sleep, disturbed concentration and affect).[4,6] Although there are secondary (objective) forms of tinnitus from organic sources, primary (subjective) tinnitus is an auditory sensation without a corresponding external sound source. It is a consequence of sensorineural hearing loss and central auditory pathway changes.[7] Advances in functional imaging have provided insight into the neural activity in normal and pathologic auditory processing pathways.[13–15] Understanding the neural mechanisms and cellular activity behind the phantom percept may refine treatment and help to develop strategies for prevention and screening.

ANATOMY OF THE AUDITORY PATHWAY

The auditory system is divided grossly into central (upper) and peripheral (lower) divisions.[16] The upper auditory pathway contains the primary auditory cortex (A1), medial geniculate bodies (MGBs), inferior colliculus (IC), superior olivary complex (SOC), and the cochlear nucleus complex (CN).[7] Components of the lower auditory pathway

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are the peripheral auditory structures; namely the pinna, external auditory canal, tympanic membrane, ossicular chain (malleus, incus, and stapes), the cochlea (hair cells, basilar membrane, and spiral ganglion), and the auditory nerve connecting the central and peripheral auditory structures.[7,16] Airborne pressure waves exert a mechanical force on the tympanic membrane that is transmitted via the middle ear ossicles to the cochlea. Mechanical energy and motion of the basilar membrane within the cochlea are transduced by an inner row of hair cells that release neurotransmitter (glutamic acid [Glu]) onto the dendrites of first-order afferent neurons. These neurons form the auditory nerve that enters and forms synapses within the CN in the brainstem.[17]

The cochlea is composed of an osseous labyrinth, a fluid-filled tunneled compartment that courses approximately 2.5 revolutions around its longitudinal axis (the modiolus) within the osseous capsule of temporal bone.[7,16,17] The scala media (cochlear duct) is a compartment enclosed by the membranous labyrinth. It contains a row of inner and 3 rows of outer hair cells laid out along the basilar membrane, along with supporting elements forming the organ of Corti.[17]

The basolateral surfaces of hair cells synapse with spiral ganglion nerve cells.[16,17] Type 1 spiral ganglion cells are large bipolar cells with myelinated fibrils that contact inner hair cells. They represent 90% to 95% of the ganglion cell population. Inner hair cells are also contacted by unmyelinated extensions arising beyond the habenula perforata.[7,16,17] Type 1 spiral ganglion cells are different from type 2 cells, which are smaller, unipolar, and mostly unmyelinated cells that contact outer hair cells.[7,16,17] Inner hair cells are primarily responsible for transducing sound, with the information reaching the brain via type 1 afferents. In contrast, outer hair cells act as modulatory amplifiers, particularly for low-level sound.[16,17]

The spiral ganglion courses through the Rosenthal canal in the central part of the cochlea.[7,16] The cochlear nerve emerges from the pontomedullary junction and courses through the internal acoustic meatus.[16,17] Most auditory nerve fibers synapse within the ipsilateral cochlear nuclei, which are tonotopically organized into anterior ventral cochlear nuclei (AVCN), dorsal cochlear nuclei (DCN), and posterior ventral cochlear nuclei (PVCN) divisions.[7] The AVCN and PVCN process the temporal features of the transmitted signal using membrane capacitance, dendritic filtering, and spatial organization, whereas fusiform cells of the DCN contribute to decoding sound level and directional information.[7,18] Integration of inputs from the somatosensory system in the DCN further improves sound localization.[4,7,13,16] The lateral lemniscus (ie, lemniscal pathway) conveys sound information from the cochlear nucleus rostral to the contralateral IC, and provides input to other nuclei as well.[7,15,16]

Most ascending connections in the IC, comprising the lemniscal pathway, synapse in the centrally located core.[7,12,16] The peripheral shell of the IC, comprising the extralemniscal pathway, receives a mixture of ascending and descending fibers.[4,5,7,13,16] The IC extracts auditory information by integrating both afferent and efferent streams (ie, lower-order and higher-order processes), sending information rostral to the thalamic MGB.[4,5,7,16] The MGB serves as an intelligent router for the auditory pathway to cortex.[7,16] The ventral subdivision of the MGB, a continuation of the lemniscal pathway, is organized tonotopically and uses fast glutamatergic synapses to connect to layers 3 and 4 of the A1.[7,19,20] Much remains to be understood about thalamocortical gating and its role in attention and arousal.

BIOCHEMICAL AND MOLECULAR TRANSDUCTION

The primary and highly preserved excitatory neurotransmitter of the brain, Glu, serves the cochlear hair cell synapses.[7,16,21] Sound-induced deflection of hair cell stereocilia affects mechanosensitive transducer channels at the apex of each hair cell.[16,17] In resting position, the ion channels are partially open, sustaining a moderate depolarizing current in the absence of stimulation.[7,13,17] Deflection of stereocilia results in the release of Glu-containing vesicles at the hair base, and depolarization of primary afferent nerves. In a conserved manner, Glu serves as the primary excitatory neurotransmitter throughout ascending levels of the auditory system.

CENTRAL NETWORK ORGANIZATION

Complex networks exist at many levels in living systems. The most efficient are selected by natural pressures.[22] Mathematical models used to analyze brain networks have shown the utility of so-called small-world organization. Small-world networks are composed of dense, semiregular cell clusters with a high degree of local connectivity and sparse long-range connections.[22–24] This network schema enables distributed, but specialized, processing that is resistant to pathologic degradation. It also provides for efficient communication and the specialized operations necessary to perform multidimensional tasks.[22] Small-world