

Peripheral tinnitus: from molecular mechanisms to therapy

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Salicylate, the active component of aspirin, is long known to produce hearing loss and tinnitus in humans and animals when used at large dose. Experiments in animals have shown that salicylate increased spontaneous activity of single units of the auditory nerve, and modified the average spectrum activity recorded from the round window, which is a gross measure of spontaneous activity of the auditory nerve (see for review Cazals, *Progress in Neurol.*, 2000, 62:583-631) suggesting that tinnitus induced by salicylate is associated with dysfunction of the auditory nerve. Based on a behavioural test, we have demonstrated that application of NMDA antagonists directly into cochlear fluids blocked tinnitus induced by salicylate, suggesting that the primary site of action of salicylate lies in the cochlea, and that salicylate acts through activation of cochlear NMDA receptors.

Testing of these hypothesis require a multidisciplinary approach based on molecular biology, pharmacology and electrophysiology, two-photon imaging and confocal and electron microscopic immunocytochemistry and complementary *in vitro* (freshly isolated spiral ganglion neurons, cochlear slices) and *in vivo* approaches to verify 1) which NMDA receptor subunits are expressed by spiral ganglion neurons, 2) which subunits are expressed at the inner hair cell sensory synapses, and 3) which of the mechanisms of action of salicylate are responsible for the modulation of cochlear NMDA receptors.

Based on these data, we will extend this approach to other animal models mimicking “real” pathologies known to induce tinnitus *in vivo* (e.g.; ischemia, presbycusis, etc.). This would provide the molecular basis for understanding and treating tinnitus that take place into the inner ear. Altogether, our results should provide clues for therapeutic targets to treat tinnitus in humans since it is now possible to introduce pharmacological agents across the round window of the cochlea in humans using various commercially available systems.

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