AUT3, a Kv3 channel modulator, counteracts elevation of spontaneous firing rates in the auditory midbrain following noise trauma

L. L. HESSE [1,4], L. A. ANDERSON[1], C. H. LARGE[5], R. SCHAETTE[2], J. F. LINDEN[3];

[1]Ear Inst., [3]Ear Inst. and Dept. of Neuroscience, Physiol. & Pharmacol., [2]Univ. Col. London, London, United Kingdom; [4]Dept. of Otorhinolaryngology, Head & Neck Surgery, Univ. of Luebeck, Luebeck, Germany; [5]Autifony Therapeutics Ltd., London, United Kingdom

Abstract:

Exposure to loud noise is a common cause of tinnitus in humans, and can be used to generate tinnitus-like behaviour and neural pathologies in animal models. Here we show that four weeks after noise exposure, mice exhibit increased spontaneous neural activity in the inferior colliculus (IC), and this elevation of spontaneous activity is normalized by intraperitoneal injections of AUT3, a novel Kv3 channel modulator. CBA/Ca mice were exposed to octave-band noise (8-16 kHz) at 105 dB SPL for two hours under anaesthesia. Four weeks later, extracellular multiunit recordings were obtained in vivo from the IC; similar recordings were made from control mice. Spontaneous multiunit activity in the IC was significantly higher in noise-exposed than in control mice. Tone-response thresholds were also significantly higher in noise-exposed mice, and distributions of characteristic frequencies and best frequencies were shifted toward lower frequencies than in control animals. Intraperitoneal injections of 90 mg/kg AUT3, a positive modulator of Kv3.1 channels, decreased IC excitability in noise-exposed animals, returning spontaneous rates to levels similar to those observed in control animals; no such effect was observed following injections of vehicle. AUT3, but not vehicle, also reduced the probability of firing to clicks and maximum click-evoked firing rates in noise-exposed animals, but had no impact on frequency tuning or thresholds of IC responses. In control animals, there were no significant differences in spontaneous rate, sound-evoked firing, or tone-response thresholds between animals receiving 90 mg/kg AUT3 and animals receiving vehicle. These results indicate that four weeks after noise exposure, spontaneous activity is elevated in the IC; that the positive Kv3 channel modulator AUT3 counteracts this increase in spontaneous activity; and that AUT3 has minimal impact on IC responses in control animals. AUT3 is therefore a potentially promising treatment for neural pathologies that may underlie tinnitus.