Abstract

KCTD12 proteins are auxiliary subunits of inhibitory $GABA_B$ receptors, regulating their surface expression and signaling kinetics. Previous findings have suggested that KCTD12 might represent a susceptibility gene for the induction of disorders such as tinnitus, but its function in the auditory system has not been elucidated. The present thesis focuses on studying the importance of the KCTD12 protein for mammalian auditory function using mice with genetic ablation of KCTD12. The effect of deletion on cochlear function and the activity of neurons in the auditory pathway of mice was assessed using a combination of acoustic, electrophysiological and behavioural methods. We measured otoacoustic emissions, evoked brainstem potentials, the startle response and its modulation by various pre-pulses and compared the obtained parameters in control WT and KCTD12-/- mice. The results showed that deletion of KCTD12 in mice led to significant changes in acoustically evoked responses of the cochlear apparatus and brainstem. KCTD12-/- mice exhibited increased audiometric thresholds, reduced amplitudes, and limited dynamic range of DPOAEs and ABRs. These changes were characterized by a striking spectral dependence, with the greatest differences between the WT and KCTD12-/- groups observed in the mid- and high-frequency regions of acoustic stimulation. These findings support the hypothesis that the KCTD12 protein plays an important role in both cochlear homeostatic mechanisms, necessary for proper OHC function, and in the central auditory pathway, where it helps maintain physiological $GABA_B$ receptor function. Consistent with this assumption, behavioral testing of auditory function revealed that KCTD12-/- mice exhibit significantly increased ASR amplitude and reduced ASR sensitivity to inhibition by a gap pre-pulse. These observations suggest the presence of audiological states such as hyperacusis and tinnitus and support the idea that deletion of KCTD12 leads to attenuation of GABAergic inhibition, disruption of the balance between excitation and inhibition, and hyperactivity of neurons in the auditory system. Thus, our results collectively demonstrate that KCTD12 deletion leads to sensorineural hearing loss and suggest that KCTD12-/- mice could serve as an animal model for investigating the mechanisms of hearing loss.

Key words: GABA-B receptor, KCTD12, hearing, tinnitus