The role of type II spiral ganglion neurons in the regulation of hearing sensitivity via the medial olivocochlear efferent pathway

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It is well established that efferent feedback from a population of neurons originating in the medial superior olive in the brainstem and synapsing onto the cochlear outer hair cells (OHC) can reduce the cochlear amplifier effect of OHC and confer protection from noise-induced hearing loss as well as regulating hearing selectivity. The majority of these medio-olivocochlear (MOC) fibres innervate the cochlea contralateral to their site of origin and this system is activated most strongly by contralateral noise. It has however, as yet, not been established whether this efferent activity is driven by the type I spiral ganglion neuron (SGN) and/or type II SGN input to the efferent MOC neurons. We sought to investigate the putative role of the type II SGN in this principal neural feedback pathway using a peripherin knockout mouse model. Peripherin is a neuronal type III intermediate filament protein, which from establishment of the afferent innervation of the sensory hair cells in the mouse cochlea, is only expressed in the type II SGN. We have previously shown *in vitro* that the BDNF-driven neurite outgrowth of type II SGN is affected by loss of peripherin expression (Barclay *et al.*, 2010). We therefore investigated the possibility that in peripherin knockout mice, the type II SGN innervation of the OHC may be disrupted and if type II SGN indeed are the principal driver for MOC activation, then contralateral suppression may be impacted. Happily, our studies support this tenet.

We used the quadratic (f1-f2) distortion product otoacoustic emission (DPOAE) and contralateral sound stimulation to study the effects of contralateral noise on the MOC efferent system in peripherin KO mice and wild type controls. Baseline hearing thresholds were also measured using DPOAE and auditory brainstem responses (ABR) to click as well as a range of pure tones. These experiments were conducted on mice under ketamine(40mg/kg)/xylazine(8mg/kg)/acepromazine(0.5mg/kg) anaesthesia in accordance with ACEC approval 07/128. Using this model we established that, despite having normal baseline hearing (DPOAE and ABR), the peripherin knockout mice largely lack the contralateral suppression of OHC transduction which is evident in wildtype mice. Wild type mice showed a strong 65±10% suppression of the DPOAE (P= 0.027 paired t-test) whereas only a 15±8% suppression was observed in peripherin KO mice. Disruption of the type II SGN innervation of the OHC was confirmed by immunolocalization of the OHC ribbon synapses (CtBP2 antibody) on cochear cryosections (peripherin KO mice (n = 6) *vs* wildtype mice (n = 5).

This evidence strongly supports the role of type II SGN afferents as the principal sensory input driving contralateral suppression in the cochlea. This small sub-population of neurons (5% of the total SGN), are therefore critical for determining the dynamic regulation of hearing sensitivity and conferring protection against noise induced damage.

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