Upregulation of ecto-nucleoside triphosphate diphosphohydrolases 1 and 2 in noise-exposed rat cochlea

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Extracellular ATP acting via P2 receptors in the inner ear initiates a variety of signalling pathways that may be involved in noise-induced cochlear injury (Thorne *et al*., 2002). NTPDase1/CD39 and NTPDase2/CD39L1 are key elements for regulation of extracellular nucleotide concentrations and P2 receptor signalling in the cochlea (Vlajkovic *et al*., 1999, 2002). This study characterised the effect of noise exposure on regulation of NTPDase1 and NTPDase2 expression in the cochlea using a combination of real-time RT-PCR, immunohistochemistry and functional studies. Adult Wistar rats were exposed to broad band noise at 90 dB and 110 dB sound pressure level (SPL) for 72 hours. Their auditory function was assessed by auditory brainstem response to clicks and pure tones. Exposure to 90 dB SPL induced a small and temporary change of auditory thresholds (temporary threshold shift), whilst exposure to 110 dB SPL induced a robust and permanent change of auditory thresholds (permanent threshold shift). NTPDase1 and NTPDase2 mRNA transcripts were upregulated in the cochlea exposed to 110 dB SPL, whilst mild noise (90 dB SPL) altered only NTPDase1 mRNA expression levels. Changes in NTPDase expression did not correlate with levels of circulating corticosterone, implying that the upregulation of NTPDase expression was not stress-related. Quantitative immunohistochemistry in the cochlea exposed to 110 dB SPL localised the increased NTPDase1 and NTPDase2 expression in the stria vascularis and upregulation of NTPDase2 in the intraganglionic spiral bundle. Whilst NTPDase1 was upregulated in the secretory tissues of the lateral wall, it was down-regulated in the cell bodies of the spiral ganglion neurones. Tissue distribution of NTPDases was not altered in the cochlea exposed to 90 dB SPL, implying a differential regulation of NTPDase expression in the cochlea in response to different noise levels. Functional studies revealed increased ectonucleotidase activity in the cochlea after exposure to 110 dB SPL, consistent with upregulation of NTPDases. These data indicate that the regulation of NTPDase1 and NTPDase2 expression in the cochlea is responsive to noise as a stimulus that also upregulates P2 receptor signalling pathways. The changes in NTPDase expression may reflect compensatory responses of cochlear tissues to limit ATP signalling during noise exposure and protect the cochlea from noise.

Thorne, P.R., Muñoz, D.J.B., Nikolic, P., Mander, L., Jagger, D., Greenwood, D., Vlajkovic, S.M., Housley, G.D. (2002) *Audiology & Neuro-Otology,* 7:180-184.

Vlajkovic, S.M., Housley, G.D., Greenwood, D., Thorne, P.R. (1999) *Molecular Brain Research,* 73:85-92.

Vlajkovic, S.M., Thorne, P.R., Sévigny, J., Robson, S.C., Housley, G.D. (2002) *Hearing Research,* 170:48-59.

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