

Potential use of estetrol in sensorineural hearing loss protection

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Introduction and Aims: Estrogens have a positive impact on the auditory function. Indeed, estradiol (E2) treatment in animals protects against acoustic trauma and aminoglycoside toxicity and its depletion can contribute to age-related hearing loss. However, estradiol is not suitable in clinical practice, given the increased risk of cancer and thromboembolic events. There is a need to find new treatments that present a higher benefit/risk ratio. In this work, we studied a new natural estrogen derivative, estetrol (E4), that was shown to act as a Selective Estrogen Receptor Modulator (SERM). Estetrol is thus able to display estrogen-like as well as antiestrogen activity depending on the target tissue. Interestingly, E4 allows the prevention of menopause symptoms such as osteoporosis or hot flushes through an agonistic action, whereas it exerts anti-estrogenic effects on the mammary gland. These preclinical data suggest that E4 presents a safer profile than E2.

Material and Methods: To investigate whether this molecule presents otoprotective actions, we exposed P2 cultured organs of Corti to gentamicin, with or without estetrol (E4). After 48 hours of culture, hair cell survival was evaluated following anti-myosin VII Immunohistochemistry. We next moved on to *in vivo* studies using young zebrafish larvae (5dpf), since they constitute a highly effective model to determine the potential ototoxicity of drugs and to screen for candidates of hair cell protective agents. We monitored the survival of hair cells within neuromasts following chronic or acute exposure to gentamicin.

Results: In cochlear culture, gentamicin-induced hair cell loss was significantly reduced by E4. Interestingly, the toxicity of aminoglycoside was also reduced *in vivo* upon treatment of zebrafish larvae with E4.

Conclusion: The survival rate of hair cells was increased in the presence of estetrol both *in vitro* and *in vivo* indicating that estetrol constitutes an interesting protective drug against hearing loss.