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Effect of chronic estradiol administration on vimentin and GFAP immunohistochemistry within the inner ear

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ABSTRACT

Recent data show that hormone replacement therapy, involving estrogen together with progestin, can promote hearing loss (Guimaraes, P., Frisina, S.T., Mapes, F., Tadros, S.F., Frisina, D.R. and Frisina, R.D., 2006. Progestin negatively affects hearing in aged women. Proc. Natl. Acad. Sci. USA. 103, 14246–14249.). But long-term estradiol treatment, which induces hyperprolactinemia in guinea pigs, results in hearing loss and bone dysmorphology of the otic capsule—without much hair cell loss (Horner, K.C., Cazals, Y., Guieu, R., Lenoir, M. and Sauze, N., 2007. Experimental estrogen-induced hyperprolactinemia results in bone-related hearing loss in the guinea pig. Am. J. Physiol., Endocrinol. Metab. 293, E1224–1232.). Since estrogen receptor β can protect the mouse cochlea against acoustic trauma (Meltser, I., Tahera, Y., Simpson, E., Hultcrantz, M., Charitidi, K., Gustafsson, J.A. and Canlon, B., 2008. Estrogen receptor beta protects against acoustic trauma in mice. J. Clin. Invest. 118, 1563–1570.), we hypothesized that estradiol might activate protective glial-like elements in the inner ear. Immunohistochemistry showed down-regulation of vimentin within the lateral wall and upregulation within the spiral limbus. Glial fibrillary acid protein was increased in the inner sulcus, Hensen cells and Claudius cells. Furthermore, there was increased expression of vimentin in type II cells of the spiral ganglion and type I vestibular hair cells. The observations suggested that estradiol treatment may affect the inner ear ionic homeostasis but protection may be afforded via activated intermediate filaments.

Introduction

Osteoporosis in aging women (Riggs et al., 1969) and men (Riggs et al., 2002) is related to decrease in estrogen. It can be prevented by hormone replacement therapy (HRT) (Lindsay et al., 1976). However, HRT has been linked to breast cancer, coronary heart disease (Rossouw et al., 2002; Beral, 2003) and increase in risk of dementia (Shumaker et al., 2003; Shumaker et al., 2004). Recent data show that HRT, involving estrogen and progestin, can cause hearing loss (Guimaraes et al., 2006). Understanding the mechanisms underlying estrogen-induced inner ear pathology could throw light on the sensitivity of the inner ear to hormones.

Various aspects of hearing function are gender specific, for example men and women are more sensitive to low and high frequencies, respectively (Pearson et al., 1995). Age-related hearing loss begins around 30 years in men and 50 years in females (Pearson et al., 1995; Gordon-Salant, 2005) indicating that estrogen might protect hearing of women up to the menopause. Interestingly, features of otoacoustic emissions change in women taking the pill (McFadden, 2000) or in transsexual males during estrogen treatment (McFadden et al., 1998).

Estrogen receptors (ERα and ERβ) are expressed in the inner ear of rodents (Stenberg et al., 1999) and humans (Stenberg et al., 2001; Hultcrantz et al., 2006). Fluctuation in hormones, within the menstrual cycle, is reflected in fluctuating hearing sensitivity (Cox, 1980; Andrews et al., 1992; Caruso et al., 2003) and postural instability (Darlington et al., 2001). Contraceptive pill (Okulicz, 1978; Dvorak, 1980; Hanna, 1986) as well as HRT (Strachan, 1996) have been linked to reports of sensorineural hearing loss. On the other hand, there appears to be no potentiating effect of the pill on various ear diseases (Vessey and Painter, 2001). In rodents, estrogen treatment changes the latency of auditory brainstem responses (Cooper et al., 1999). Long-term estrogen treatment results in deterioration of hearing and morphopathology of the stria vascularis (Bittar et al., 2001). Estradiol-induced hearing loss in guinea pigs, sets in earlier in males than females and in the long-term both present similar dysmorphology of the otic capsule in the absence of substantial hair call loss (Horner et al., 2007).

There is good evidence that estrogen can protect neurons in-vivo and in-vitro (McEwen and Alves, 1999). In addition, a substantial body of recent research now shows that glia have estrogen receptors, and estrogen modulates astrocyte function (Mong and Blutstein, 2006). Indeed estrogen may have a key role in neuronal protection (Jordan, 1999) by coordinating neuronal–glia interactions (Struble et al.,

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2007). Upregulation of intermediate filaments (Eng and Ghirnikar, 1994) appears to be a crucial step in astrocyte activation which helps protect neurons in the acute stage (Pekny et al., 1999). In contrast, absence of glial fibrillary acid protein (GFAP) and vimentin prevents reactive gliosis and could improve post-traumatic regeneration (Wilhelmsson et al., 2004). We hypothesized that activated astrocyte-like elements within the inner ear, during chronic estradiol administration, might reflect an activated protection system—contributing to the preservation of hair cells.

Materials and methods

Animal preparation

The experimental procedures were carried out under the licence from the French Ministry of Agriculture to K.C.H. The care and use of the animals used here were in accordance with the European Communities Council (86/609/EEC) for care and use of laboratory animals. Young adult pigmented guinea pigs (250 g) were employed

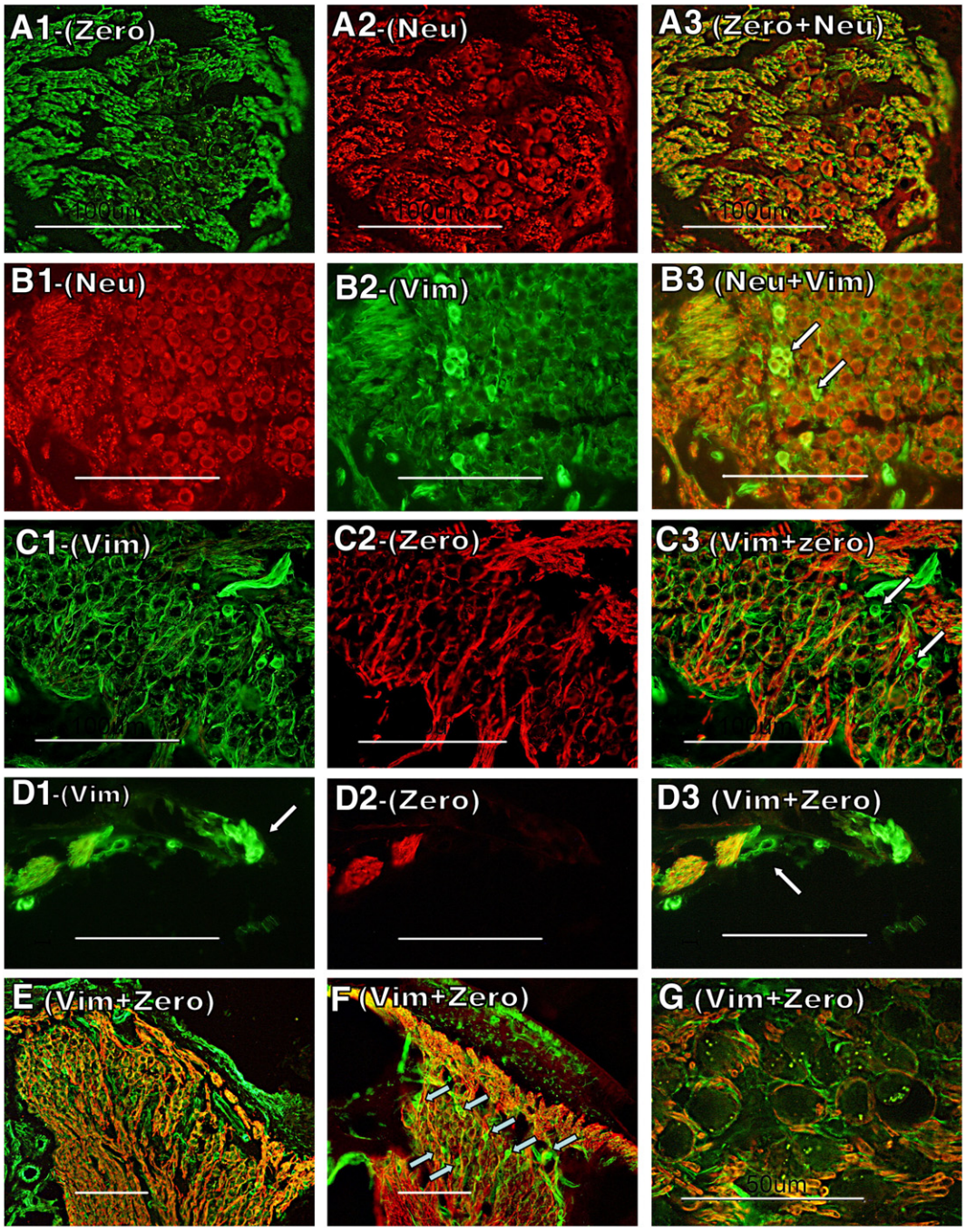

Fig. 1. Cross section of the spiral ganglion of the cochlea in control (D, E, G) and estradiol-treated (A, B, C, F) animals. Labeling of compact myelin (Zero, A1), neurofilaments (Neu, A2) and double labeling (A3) is in keeping with the fact that the majority of cochlear nerve fibres and spiral ganglion cells are myelinated. Labeling of neurofilaments (Neu, B1) and Schwann cells (vimentin, B2) and double labeling (B3) shows that Schwann cells ensheathe the spiral ganglion cells. Double labeling with vimentin (C1) and Zero (C2) confirms the colocalization for the most part (C3). Some vimentin-alone labeling is also observed, indicating non-myelinating Schwann cells or non-compact myelin. Myelinated and non-myelinated fibres can be seen to be intermingled at the level of the spiral ganglion (C3, G). As the afferent fibres emerge from the habenula, the labeling of the Schwann cells (vimentin, D1) spatially precedes that of myelin (Zero, D2) as seen in double labeling (arrow, D3), in keeping with the fact that all auditory nerve fibres are unmyelinated within the organ of Corti. Deiters cells are also typically labeled with vimentin (arrow, D1). Small vimentin-labeled cells bodies, likely to be type II, can be readily observed in estradiol-treated animals (arrows, B3, C3, F) but rarely and discretely labeled in controls (E). Scale bars are 100 μm in all figures except G where it represents 50 μm.