

Oestrogen, ocular function and low-level vision: a review

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Abstract

Over the past 10 years, a literature has emerged concerning the sex steroid hormone oestrogen and its role in human vision. Herein, we review evidence that oestrogen (oestradiol) levels may significantly affect ocular function and low-level vision, particularly in older females. In doing so, we have examined a number of vision-related disorders including dry eye, cataract, increased intraocular pressure, glaucoma, age-related macular degeneration and Leber's hereditary optic neuropathy. In each case, we have found oestrogen, or lack thereof, to have a role. We have also included discussion of how oestrogen-related pharmacological treatments for menopause and breast cancer can impact the pathology of the eye and a number of psychophysical aspects of vision. Finally, we have reviewed oestrogen's pharmacology and suggest potential mechanisms underlying its beneficial effects, with particular emphasis on anti-apoptotic and vascular effects.

Key Words

- ▶ oestrogen
- ▶ menopause
- ▶ eye
- ▶ vision

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Introduction

Emerging evidence suggests that appropriate levels of the sex steroid hormone oestrogen (and in particular oestradiol (E₂)) may be a significant factor in the maintenance of healthy visual function, particularly in older females. To our knowledge, with the exception of one Cochrane database study (Gharaibeh *et al.* 2011), which reviewed the use of oestrogen in treating traumatic hyphema (injury-related blood in the anterior chamber of the eye), there are no recent reviews on the use of oestrogen in the treatment of visual dysfunction in older adults. In this review, we examine evidence for oestrogen's importance in human vision, with particular emphasis on its potential as a therapeutic target in postmenopausal vision.

Oestrogen and its pharmacology

There are three main types of oestrogen (Fig. 1): oestrone (E₁), E₂ and oestriol (E₃), and their levels are determined by

oestrus cycle, age and pregnancy. E₁ is most abundant during menopause and post-menopause, E₂ in younger (<45 years) women and E₃ during pregnancy. There are also numerous other naturally occurring oestrogens. Although the remit of this review concerns the relationship between oestrogen and vision in females, it is worth noting for completeness that oestrogens are also present in males. Indeed, they play a major role in many metabolic functions in men (de Ronde *et al.* 2003). It has even been suggested that many biological effects attributed to testosterone may actually represent the effects of oestrogens (de Ronde *et al.* 2003). Although, like females, oestrogen levels decline in older men, the decline is relatively modest (Orwoll *et al.* 2006). Furthermore, older (more than 65 years) males may actually have higher E₂ levels than their older female counterparts (Carlson & Sherwin 2000).

Oestrogens can easily diffuse across cell membranes and act on the cytosolic oestrogen receptors, ER α (ESR1)

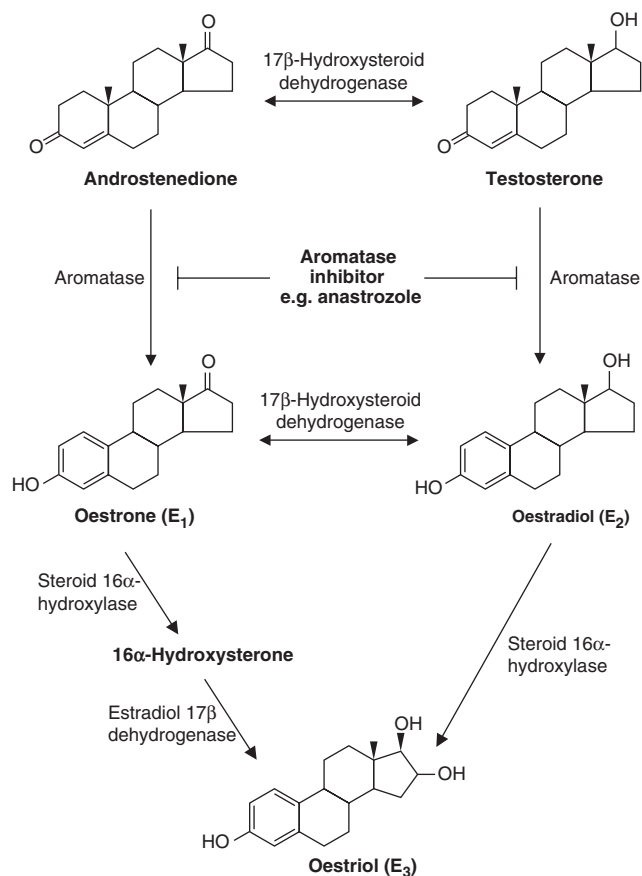


Figure 1

Synthesis of oestrogens. Structures of the three main types of oestrogen are shown: E_1 , oestradiol (E_2) and E_3 . Oestrogens are synthesised from androgens, testosterone and androstenedione, by the enzyme aromatase. The aromatase inhibitor anastrozole is used in the treatment of breast cancer after surgery to inhibit the synthesis of oestrogens. Oestrogens are produced primarily in the ovaries, but also in smaller amounts in liver, adrenal glands, breast and neurons.

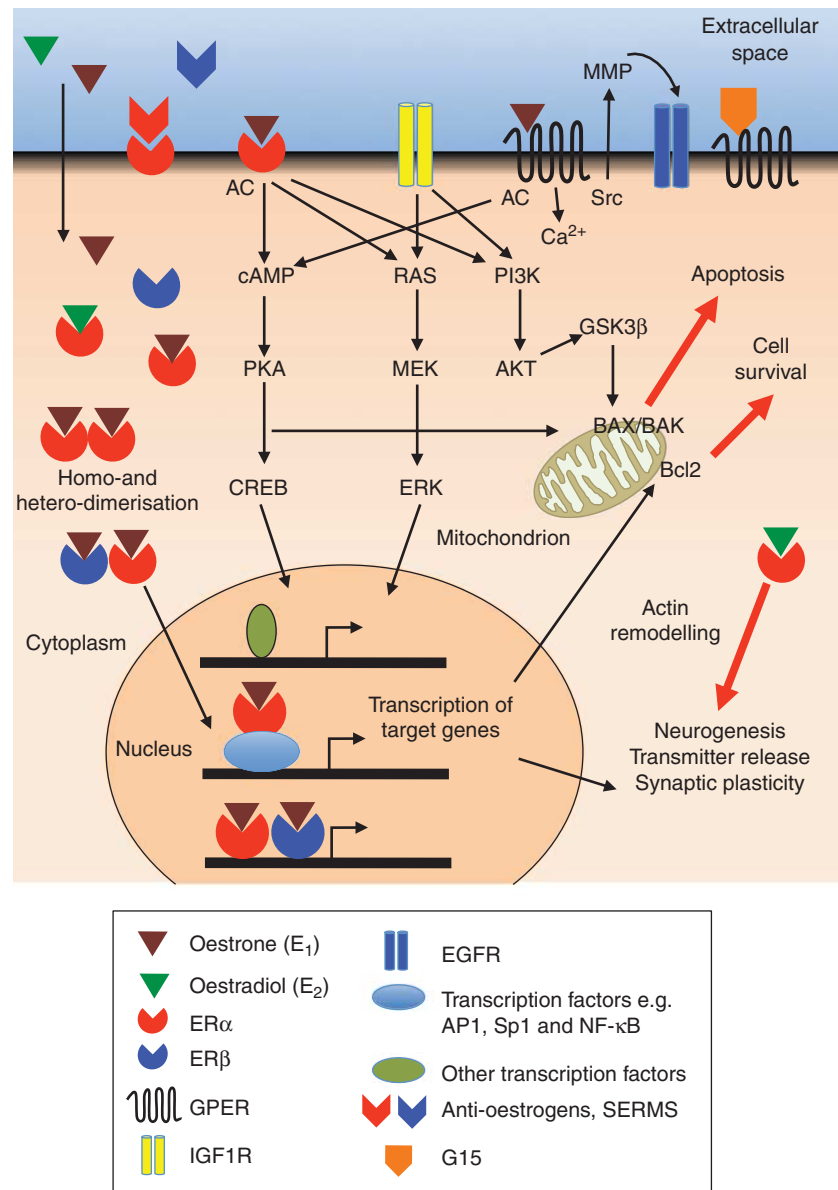
and $ER\beta$ (ESR2). Oestrogens and their receptors (ERs) regulate diverse signalling pathways to modulate neuronal differentiation, influence cell migration, survival and death, and synaptic plasticity of neurons (Fig. 2; Arevalo *et al.* 2011). The mechanisms of oestrogen action include both nuclear-initiated cell-signalling and membrane/cytoplasm-initiated cell-signalling. In the absence of a ligand, the classical ERs ($ER\alpha$ and $ER\beta$) are predominantly cytosolic. Upon oestrogen activation, they relocate to the nucleus and interact with *cis*-regulatory elements of target genes by directly binding to oestrogen-response elements (EREs) or indirectly through their interaction with other DNA-bound transcription factor complexes. The ERs thereby facilitate the transcription of target mRNAs, including those encoding proteins important for cell survival and neuronal function. Recently, a

G protein-coupled oestrogen receptor (GPER – previously known as GPR30) has been identified, which acts at the cell surface and is found in a variety of tissues (Hazell *et al.* 2009, Filardo & Thomas 2012). Whereas the nuclear receptors mediate the long-term ('genetic') effects of oestrogen, GPER probably mediates some of the more rapid 'pre-genomic' signalling actions. The non-classical ER, GPER, as well as a fraction of $ER\alpha$ and $ER\beta$, is located at the cell membrane and can therefore be rapidly activated upon ligand binding (Manavathi & Kumar 2006). ERs form complexes with G-proteins, glutamate receptors, receptor tyrosine kinases (RTKs), such as insulin-like growth factor 1 receptor and epidermal growth factor receptor, and non-RTKs (e.g. Src) to regulate a wide variety of cellular functions. For example, E_2 and $ER\alpha$ have recently been shown to control neuron morphology by regulating actin remodelling through extra-nuclear signalling via the RHO and RAC1 pathways (Sanchez & Simoncini 2010). By influencing the RAS/ERK, PI3K/AKT and cAMP/PKA pathways, which ultimately can affect events in the nucleus, the membrane ERs likely connect the non-genomic actions of oestrogens to its genomic responses.

The eye

Oestrogen is abundant in the mammalian eye. ERs have been found in the retina, cornea, lens, iris, ciliary body, conjunctiva, lacrimal and meibomian glands of male and female eyes across a number of species including humans, rodents and rabbits (Wickam *et al.* 2000, Gupta *et al.* 2005). It is unsurprising therefore that oestrogen levels may impact vision through its effects on the eye, from the ocular surface to the retina.

The presence of ERs in the conjunctiva, lacrimal and meibomian glands suggests that oestrogen may modulate tear production (Versura & Campos 2005). For example, the prevalence of dry eye syndrome is more common in older women compared with older men, and women with glaucoma are more likely to suffer from this condition than men (Erb *et al.* 2008). Although its causes are multifactorial, increased prevalence in older women may reflect postmenopausal oestrogen (E_2) reduction. Tear production decreases after menopause (Altintas *et al.* 2004). Although some studies have found that hormone replacement therapy (HRT) leads to a decrease in tear function (Schaumberg *et al.* 2001, Uncu *et al.* 2006), the majority have shown that dry eye improves after HRT (Affinito *et al.* 2003, Guaschino *et al.* 2003, Altintas *et al.* 2004, Taner *et al.* 2004, Coksuer *et al.* 2011). In addition, topical E_2 drops appear to alleviate dry eye symptoms

**Figure 2**

Oestrogen-regulated signalling pathways that could affect retinal function and health. The nuclear-initiated signalling response of oestrogens is mediated by the classical oestrogen receptors (ERs – ER α and ER β), which relocate to the nucleus after ligand binding and dimerisation. By binding to estrogen-response elements (ERE) at specific target genes, ERs can activate transcription. E₁ and oestradiol can also bind to ERs (ER α , ER β) and G-protein-coupled oestrogen receptor (GPER) located at the cell membrane and rapidly activate signalling pathways including the RAS/ERK, PI3K/AKT and cAMP/PKA pathways. These can influence transcription, cytoskeleton remodelling, apoptosis/cell survival as well as neuron-specific

(Sator *et al.* 1998). However, at present, there is insufficient basic experimental evidence to justify this treatment. In addition, animal studies have demonstrated increased apoptosis in ocular surface epithelial cells in rats after ovariectomy, which was reduced after 3 months of E₂

functions, such as transmitter release and synaptic plasticity. Dysregulation of these processes could be important in visual dysfunction. There is considerable cross-talk between ERs and other receptors such as insulin-like growth factor receptor (IGF1R) and epidermal growth factor receptor (EGFR). Note: oestrogen has a higher affinity for ER α than ER β . AC, adenylyl cyclase; PKA, protein kinase A; MMP, metalloproteinase; PI3K, phosphoinositide 3-kinase; GSK3 β , glycogen synthase kinase 3 β . G15 is a GPER antagonist. A full colour version of this figure available via <http://dx.doi.org/10.1530/JOE-14-0349>.

therapy (Özcura *et al.* 2012). E₂ has also been shown to ameliorate corneal epithelial inflammation in rodent models (Wang *et al.* 2012).

E₂ has also been implicated in the health of the lens. There is an apparent weak protective association between

use of oral contraceptive pill and the development of cortical cataract (Kanthan *et al.* 2010), a notion supported by evidence that E₂ treatment prevents induced cataracts in rats (Hales *et al.* 1997, Chen *et al.* 2004). In addition, patients prescribed tamoxifen, a selective ER antagonist, for the treatment of breast cancer are more likely to develop cataracts (Paganini-Hill & Clark 2000, Lee *et al.* 2004). There is also some evidence that HRT might reduce the risk of increased lens opacity and cataract development (Worzala *et al.* 2001), although this is still a matter of debate, as others report no effect (Altintas *et al.* 2004, Kanthan *et al.* 2010).

Eye disease and the retina

Oestrogen has been identified as a potential factor in age-related diseases that affect the retina, such as glaucoma and age-related macular degeneration (AMD). Indeed, a recent review has concluded that oestrogen (at the proper dose) should be considered a potential therapy for glaucoma, particularly in menopausal women who suffer from the condition (Wei *et al.* 2012). The polymorphism of *ERβ* gene is associated with intraocular pressure (IOP) elevation in female patients with open-angle glaucoma (Mabuchi *et al.* 2010), and polymorphisms of *ERβ* increase its risk in males (de Voogd *et al.* 2008). There is also evidence that early menopause (<45 years) may be associated with a higher risk of glaucoma (Hulsman *et al.* 2001). Later menopause (>54 years) has been associated with a reduced risk of developing open-angle glaucoma (Pasquale *et al.* 2007). Postmenopausal women may be more susceptible to glaucoma because of the effects of oestrogen (specifically, reduced E₂ levels) on IOP elevation. High IOP is a risk factor in the development of glaucoma. Women have significantly higher IOP than age-matched men at/after the age of menopause (Ganley 1980, Pointer 2000, Altintas *et al.* 2004). A number of studies have therefore examined the utility of HRT for lowering IOP and, by extension, reducing glaucoma risk. These studies have indicated mixed results. Some report no effect of hormone therapy on IOP (Guaschino *et al.* 2003, Abramov *et al.* 2005), and one study (Khurana *et al.* 2006) found that HRT raises IOP in postmenopausal females with dry eye syndrome. However, most studies observed that hormone therapy significantly lowers IOP in menopausal (Sator *et al.* 1998) and postmenopausal women (Guaschino *et al.* 2003, Altintas *et al.* 2004, Uncu *et al.* 2006, Tint *et al.* 2010, Coksuer *et al.* 2011; data given in Table 1). This conclusion is supported by animal models, where it has been reported that E₂ prevents retinal

ganglion cell loss induced by acute IOP elevation in rats (Russo *et al.* 2008). Studies investigating the effects of normal cycling oestrogen on IOP have been inconclusive. Although an early study suggested that IOP is highest in the menstrual phase (when oestrogen is lowest; Salvati 1923), more recent studies have shown no change across the menstrual cycle (Qureshi *et al.* 1997, Seymenoglu *et al.* 2011). Oestrogen has also been implicated in AMD in older females, where contraceptive use and postmenopausal HRT lower the risk of developing it. This is particularly the case for neovascular AMD (Haan *et al.* 2006, Feskanich *et al.* 2008).

Oestrogen has also been implicated in genetic retinal diseases such as Leber's hereditary optic neuropathy (LHON). LHON is a mitochondrial disease, caused by mutations in the genes encoding the subunits of NADH dehydrogenase within the mitochondrial genome. It is mostly prevalent in young men and is characterised by retinal ganglion cell degeneration and, consequently, optic atrophy and central vision loss. A recent study has shown that E₂ was able to ameliorate mitochondrial dysfunction in a cell model of LOHN, which includes production of reactive oxygen species and apoptosis (Giordano *et al.* 2011). This suggests that in females, oestrogens may play a protective role on mitochondrial metabolism, thereby accounting for the prevalence of LHON in male.

Visual psychophysical performance

Little attempt has been made to assess the effects of oestrogen on behavioural (psychophysical) measures of vision. The findings of the limited number of studies that have been done so far are promising, in that some aspects of visual sensitivity do vary with oestrogen levels. A phyto-oestrogen-rich diet (e.g. flax and soy) may improve the performance on short wavelength-automated perimetry in postmenopausal females (Eisner & Demirel 2011). There is also evidence that visual sensitivity improves in pregnancy, being greatest in the third trimester when oestrogen levels are at their highest (Akar *et al.* 2005). Contrast sensitivity is lower in postmenopausal than in premenopausal women (Siesky *et al.* 2008), particularly at high spatial frequencies (between 9 and 18 cycles/degree), and improves after hormone therapy (Guaschino *et al.* 2003). Contrast sensitivity may also vary with normal cycling oestrogen (Johnson & Petersik 1987), being best towards the middle of the cycle when E₂ levels in the blood are at their highest.

Table 1 Effects of hormone replacement therapy (HRT) on intraocular pressure (IOP)

HRT treatment	Treatment duration at time of testing experimental group	Cohort sizes		Effect on IOP	References
		Experimental groups	Control groups		
Oestrogen + dydrogesterone	+ 12 months	40	40	No difference between experimental and control groups	Guaschino <i>et al.</i> (2003)
Oestrogen + progesterone (95 participants)	≥ 12 months	107	107	No difference between experimental and control groups	Abramov <i>et al.</i> (2005)
Oestrogen (12 participants)					
Oestrogen + medroxyprogesterone	Pre-treatment and +6 and 12 months	19	None	No effect	Uncu <i>et al.</i> (2006)
Tibolone		6		No effect	
Oestrogen patch		5		No change after 6 months. Decrease relative to pre-therapy measurement after 12 months treatment	
Oestrogen + methylprogesterone	Pre-treatment and intermittently over 12 months	13	None	IOP increased over 12-month treatment period	Khurana <i>et al.</i> (2006)
Oestrogen + drospirenone	Pre-treatment and +6 months	34	None	Decrease relative to pre-therapy measurement	Coksuer <i>et al.</i> (2011)
Oestrogen	Pre-treatment and +3 and 6 months	24	None	Decrease relative to pre-therapy measurement. Improvement plateaued after 3 months	Affinito <i>et al.</i> (2003)
Medroxyprogesterone HRT (combination unknown)	Pre-treatment and +2 months	24	None	No effect	
		15	None	Decrease relative to pre-therapy measurement	Altintas <i>et al.</i> (2004)
Oestrogen	Variable	33	172	Lower in experimental group than in controls	Tint <i>et al.</i> (2010)
Oestrogen + progesterone		58		Lower in experimental group than in controls	

Visual side effects of breast cancer treatment

A good deal of direct evidence for the effects of oestrogen on ocular function and visual sensitivity can be found in studies of vision in those undergoing treatment for hormone receptor-positive breast cancer. Hormone receptor-positive breast cancer is typically treated pharmacologically using selective ER modulators (SERMs), such as tamoxifen, or aromatase inhibitors, such as anastrozole. Both treatments act by reducing the effects of oestrogen and both have been shown to produce visual (Eisner & Luoh 2011) and possibly some cognitive (Espeland *et al.* 2010) side effects. Tamoxifen is a selective ER antagonist. Its use, even for short periods, increases the risk of cataract (Paganini-Hill & Clark 2000, Lee *et al.* 2004), and cystoid spaces in the fovea become apparent within a year of treatment (Nayfield & Gorin 1996). It may cause optic neuritis (Noureddin *et al.* 1999, Colley & Elston 2004) and reduce the size of the optic cup, which has been attributed to astrocytic swelling caused by tamoxifen-induced oestrogen reductions (Eisner *et al.* 2007). Some women undergoing tamoxifen treatment exhibit anomalous

colour sensitivity (Eisner *et al.* 2004, Eisner & Incognito 2006, Salomao *et al.* 2007). Aromatase inhibitors are also used to treat early-stage breast cancer. The most commonly used is anastrozole, which inhibits oestrogen synthesis by binding to aromatase enzymes and interfering with steroidal hydroxylation (Fig. 1). Although SERMs such as tamoxifen are prescribed to women of all ages, aromatase inhibitors are only successful in postmenopausal women as they fail to block oestrogen production sufficiently in premenopausal patients. Although anastrozole causes fewer visual side effects than tamoxifen, anomalous colour vision is common (Eisner & Toomey 2008) and vitreo-retinal traction is increased (Eisner *et al.* 2009).

Potential mechanisms of oestrogen cell protection

The role of oestrogens as neuroprotective agents in regulating the balance between cell survival, proliferation and apoptosis is mediated by both nuclear and non-nuclear mechanisms. E₂ can modulate the expression of

the anti-apoptotic proteins BCL2 and/or BCL-XL (the long isoform of BCL-X) in neurons and, conversely, can downregulate the expression of the pro-apoptotic BAD or NIP2, a negative regulator of BCL2 (reviewed in *Simpkins et al. (2010)*). The finding that ERs, particularly ER β , localise to mitochondria suggests they play important roles in this organelle (*Klinge 2008*). Through modulating RAS/ERK, PI3K/AKT and PKA signalling pathways, as well as regulating intracellular calcium levels, oestrogen signalling can impinge upon mitochondrial function and mediate apoptosis/cell survival of neurons (*Queseda et al. 2008, Simpkins et al. 2010, Azcoitia et al. 2011, Vasconsuelo et al. 2011*). Oestrogen can also have protective effects through the brain's immune cells, microglia, and through oligodendrocytes, which help to maintain the myelination of some neurons (e.g. retinal ganglion cells) through the ER β receptor (*Crawford et al. 2010*).

ER α receptor activation is anti-inflammatory, leading to cell protection, while ER β receptor activation may facilitate recovery (*Tiwari-Woodruff & Voskuhl 2009*). These effects may be mediated through an inhibition of apoptosis (*Jover-Mengual et al. 2007, Yang et al. 2010*). E₂ protects against retinal ganglion cell death (*Nakazawa et al. 2006*) and glutamate-induced toxicity (*Yamashita et al. 2011, Nixon & Simpkins 2012*) in rodents. It increases retinal blood flow and protects the retinal nerve fibre layer in ovariectomised rats (*Deschênes et al. 2010*) and prevents swelling in rat retinal glial cells (*Neumann et al. 2010*). Genistein, an isoflavone that binds to ERs, protects the retina against ischaemia (*Kamalden et al. 2011*) and the ER β -selective agonist GTx-822 protects retinal pigment epithelial cells from oxidative stress-induced apoptosis (*Giddabasappa et al. 2010*). Similar effects have been shown for the oestrogen agonist paeoniflorin (*Wankun et al. 2011*).

The protective effects of oestrogen levels in the blood vessels (*Fig. 3*) may be particularly important for visual diseases such as glaucoma, for which ocular hypertension is a significant risk factor (*Gordon et al. 2002, Kass et al. 2002*). Indeed, this account fits with the notion that use of HRT and contraceptive pill protects against neovascular AMD (*Haan et al. 2006, Feskanich et al. 2008*). Oestrogen interacts with endothelial cells, which surround the lumen of blood vessels, and smooth muscle cells, which control contraction of blood vessels. Within blood itself, oestrogen interacts with platelets, involved in haemostasis, and leukocytes, the blood's immune cells (*van der Spuy & Pretorius 2012*). Indeed, some of the protective effects of oestrogen on ocular function may be due to its direct positive effects on arterial function. In humans,

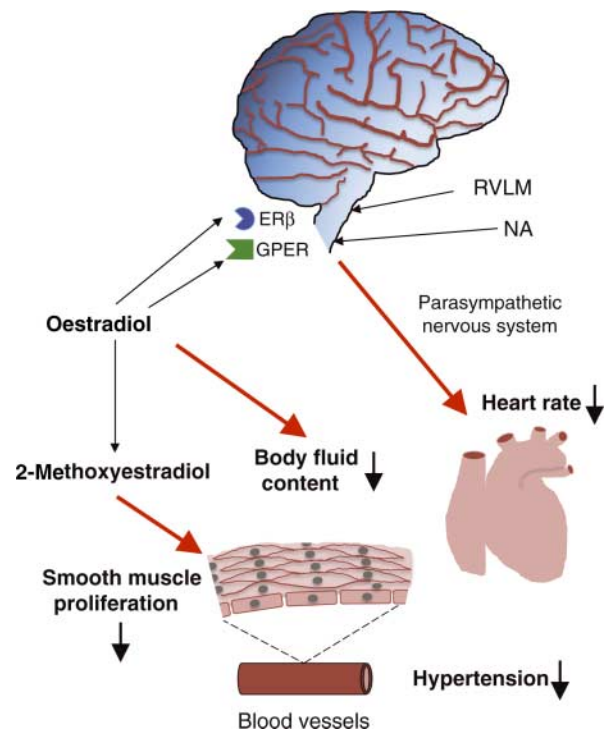


Figure 3

Putative cardiovascular effects of oestrogen. Oestradiol activates two brain areas to decrease heart rate via the parasympathetic nervous system. The rostral ventrolateral medulla (RVLM) is activated via ER β receptors and the nucleus ambiguus (NA) is activated via GPER. This decreased heart rate might decrease hypertension-related visual pathologies. One oestradiol metabolite is 2-methoxyestradiol, which can decrease smooth muscle cell proliferation in blood vessels, also reducing hypertension. A full colour version of this figure available via <http://dx.doi.org/10.1530/JOE-14-0349>.

choroidal circulation is lower in postmenopausal women compared with pre-menopausal women (*Kavroulaki et al. 2010*), and hormone therapy has been shown to improve blood flow in the inferotemporal retinal artery, peripapillary retina and the optic nerve head rim. Similar effects have been observed in rats treated with E₂. Increased retinal blood flow increases optic nerve head rim volume in postmenopausal women (*Deschênes et al. 2010*). It has also been suggested that changes in ocular (retinal and choroidal) blood flow may affect visual characteristics such as contrast sensitivity (*Shoshani et al. 2011*). This is important given that contrast sensitivity decreases after menopause, improves after HRT and is affected by normal cycling oestrogen. Coupled with evidence that reduced retinal blood flow may act as a precipitant in the development of glaucoma and AMD (*Harris et al. 1999, Flammer et al. 2002, Pinto et al. 2012*), these findings support the idea that post-menopausal oestrogen deficiency may, at least circuitously, dispose older females to these age-related ocular diseases.

Some caveats

Much of the work concerning oestrogen (particularly E₂) and its role in human vision have concentrated on the effects of menopause and HRT on visual function. A few studies have also examined the effects of normal cycling oestrogen. The most clear-cut evidence is from studies that have examined the effects of ER positive breast cancer medications (e.g. SERMs) on visual function. Although the majority of studies suggest that oestrogen regulates a range of ocular functions, a clear consensus has yet to emerge. Many of the clinical studies we have reviewed are limited by relatively low numbers of subjects and/or may not have appropriate control groups. Thus the conclusions of these studies must be accepted with these limitations.

Although numerous studies have suggested that oestrogen may be neuroprotective (Azcoitia *et al.* 2011), and many of the studies we reviewed here suggest that it may be a treatment option in some types of visual dysfunction, this may be a too simplistic view. The Women's Health Initiative (WHI) study on the use of HRT in the USA is a case in point. This study was carried out in postmenopausal women who were treated with conjugated equine oestrogens plus medroxyprogesterone and followed up for 5.2 years only to find that HRT increased the risk of coronary heart disease, breast cancer, stroke and pulmonary embolism (Rossouw 2002). A similar study in the UK came to the same conclusions (Million Women Study; Million Women Study Collaborators 2003). Other studies suggest that giving replacement therapy immediately after menopause may be beneficial (Maki *et al.* 2011), but that waiting too long after menopause may cause problems (Sherwin 2006, Selva-manj & Sohrabji 2010). The effects of dose and timing of oestrogen treatment in aged females have been reviewed (Azcoitia *et al.* 2011, Foster 2012) and have been suggested that age-related changes in ER α /ER β expression, in addition to a reduction in E₂, may affect transcription, neuronal growth and neuroprotection (Foster 2012). Another issue in elderly women is the increased number of ER α -splice variants, leading to a decline in ER α function (Ishunina & Swaab 2008). Concomitant treatment with other hormones may be protective, for example the use of oestrogen with progesterone (Acs *et al.* 2009). On the other hand, some combination therapies may be counterproductive (Irwin *et al.* 2011). Thus, treating visual dysfunction with oestrogen-related drugs may not be a simple procedure.

Although most research has focused on the well-known nuclear ERs ER α and ER β , recent research has

identified at least one cell-surface GPER and it is possible that other orphan receptors are also targets for oestrogen. It should be noted that G protein-coupled receptors are likely to down-regulate with chronic E₂ treatment (Cheng *et al.* 2005, Hatsumi & Yamamuro 2006), but this is not always the case (Navarro *et al.* 2013). In addition, some studies have found ER α to be located in the cell membrane, and these cell membrane ERs will be faster acting than nuclear ERs.

Conclusions and future directions

On balance, there is emerging support that endogenous oestrogen plays an important role in ocular pathology and low-level vision. In particular, postmenopausal oestrogen deficiency may lead to increased IOP, which may, in turn, leave older women at increased risk of developing ocular diseases such as glaucoma. In the absence of large-scale and longitudinal studies in humans, there is some way to go before a direct causal link between oestrogen deficiency and visual dysfunction is conclusively established.

Finally, in describing potential cellular protective effects of oestrogen, we have cited many studies from the field of neurobiology, rather than ophthalmology. Apart from the fact that there are many more neurobiology studies describing the protective effects of oestrogen, our reasoning for doing this was that many of the cells in the retina can be considered neuronal and it is likely that many of the mechanisms and intracellular pathways described are important in the eye. To fully understand oestrogen's role in retinal function and health, a major challenge will be to determine the relevant molecular targets. These may be both direct and indirect transcriptional changes and could include miRNAs; ERs can also have repressive, as well as activating, effects at specific promoters. Epigenetic regulation at EREs, which has recently been shown to control oestrogen signalling in breast cancer (Hervouet *et al.* 2013), adds a further level of complexity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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