Steroids 103 (2015) 31–41

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

The estrogenic retina: The potential contribution to healthy aging and age-related neurodegenerative diseases of the retina

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ARTICLE INFO

Article history:
Received 15 March 2015
Received in revised form 29 July 2015
Accepted 4 August 2015
Available online 8 August 2015

Keywords:
Retinal neurosteroidogenesis
Oestradiol synthesis and receptors
Cholesterol-metabolizing P450s
P450 aromatase
Retinal neurodegenerative diseases

ABSTRACT

These last two decades have seen an explosion of clinical and epidemiological research, and basic research devoted to envisage the influence of gender and hormonal fluctuations in the retina/ocular diseases. Particular attention has been paid to age-related disorders because of the overlap of endocrine and neuronal dysfunction with aging. Hormonal withdrawal has been considered among risk factors for diseases such as glaucoma, diabetic retinopathy and age-related macular disease (AMD), as well as, for Alzheimer's disease, Parkinson's disease, or other neurodegenerative disorders. Sex hormones and aging have been also suggested to drive the incidence of ocular surface diseases such as dry eye and cataract. Hormone therapy has been approached in several clinical trials. The discovery that the retina is another CNS tissue synthesizing neurosteroids, among which neuroactive steroids, has favored these studies. However, the puzzling data emerged from clinical, epidemiological and experimental studies have added several dimensions of complexity; the current landscape is inherently limited to the weak information on the influence and interdependence of endocrine, paracrine and autocrine regulation in the retina, but also in the brain. Focusing on the estrogenic retina, we here review our knowledge on local 17β-oestradiol (E2) synthesis from cholesterol-based neurosteroidogenic path and testosterone aromatization, and presence of estrogen receptors (ERα and ERβ). The first cholesterol-limiting step and the final aromatase-limiting step are discussed as possible check-points of retinal functional/dysfunctional E2. Possible E2 neuroprotection is commented as a group of experimental evidence on excitotoxic and oxidative retinal paradigms, and models of retinal neurodegenerative diseases, such as glaucoma, diabetic retinopathy and AMD. These findings may provide a framework to support clinical studies, although further basic research is needed.

1. Introduction

Since the discovery of brain neurosteroids in 1981 by Corpechot et al. [1], studies have been undertaken to investigate the likelihood that neurosteroidogenesis may occur also in the retina as part of the central nervous system. Consistent with the definition of a steroidogenic tissue, the retina was found to transform cholesterol into pregnenolone and then in the derived steroids (progestogens, corticosteroids, and sex steroids) [2,3] Enzymes of the neurosteroidogenic pathway were found at different retinal cells in a context of functional and dysfunctional networks, conceivably with a role of their neurosteroid products in the visual function. Other eye regions were also seen to be capable to metabolize circulating steroids [4]. Subsequently, it was discovered that the 17β-oestradiol (E2) is locally formed in the retina via a cholesterol-based synthesis and testosterone aromatization [2,5]. As well, estrogen, androgen, progesterone, mineralocorticoid and glucocorticoid receptors were identified throughout the eye regions, including the retina [5,6–12]. These findings opened up new avenues of the eye research, revealing previously unknown signaling substrates, the neurosteroids, and the likelihood that locally synthesized neurosteroid E2 could influence visual processing and eye diseases.

In these last two decades, the potential use of sex hormone therapy in the treatment of several neurological and eye diseases, especially age-related diseases, has spurred the interest of researchers towards translational rather than basic research, leading to many unresolved questions. Studies have primarily focused the influence of gender, hormonal fluctuations and on the effects of hormone therapies in retinal/ocular diseases, from the clinical and epidemiological points of view (for reviews, see Refs. [13–15]). Experimental studies have approached the effects of exogenous E2 in retinal disease conditions, the mechanisms of which remain elusive. However, the conflicting results obtained from these studies have pointed out a high complexity and important caveats

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http://dx.doi.org/10.1016/j.steroids.2015.08.002
0039-128X/

concerning the correlation of sex hormones to diseases and treatments, if estrogen is neuroprotective, inefficacious or even harmful upon certain circumstances.

These studies have also concerned glaucoma, diabetic retinopathy and AMD that are the principal causes of irreversible blindness in the world. They are featured by vascular defects, often associated with pathological neovascularization, and neurodegenerative processes. These diseases are properly identified as retinal neurodegenerative disorders, and they share with the canonical neurodegenerative diseases the frequent occurrence in elderly people, the potential link with gender and sex hormones, and many dysfunctional mechanisms ending in neurodegeneration. The hormonal withdrawal during menopause has emerged as a risk for their occurrence, like for many neurodegenerative diseases, albeit data are not conclusive. Clinical results from estrogen therapy (either alone or combined with progesterone) are also controversial. For more detailed information concerning these topics, readers are referred to some recent reviews [13,15–18,19–22].

The especial attention towards the influence of circulating hormones in these diseases has neglected the ability of retina and other ocular structures to endogenously synthesize *ex novo* or metabolize sex hormones. The recent literature underlines the lack of adequate information on the local milieu of steroids and, especially sex steroids. Circulating hormones released into the retina from vascular endothelial cells and surrounding tissues, and locally synthesized neurosteroids might play a key role in regulating neuronal activity and blood flow over the light responses as a result of an autocrine/paracrine controlling device. Fundamental questions are whether local neurosteroidogenesis may impact the physiology and pathology of the retina/ocular tissues and if circulating and local neurosteroids/sex steroids may result in opposite or equal, but complimentary, effects. Studies on the local estrogenic capability of the retina could help to define strategic routes of estrogen benefits, potentially valuable for retina and brain neurodegenerative diseases. Here, we provide an overview of the oldest and latest observations on the retinal neurosteroidogenesis, primarily on estrogen genesis and function, to comprehend and expand the view of how local estrogen may correlate with retinal diseases.

Before going into the scope of this review article, a brief summary on the retinal organization in terms of neural cell types and vascularization is given below.

2. The retina

The retina develops into a layered array of different cell types: photosensitive cells, various types of neurons (bipolar cells, ganglion cells, amacrine cells, horizontal cells), and glial cells. The vast majority of retinal synapses use glutamate for the light transmission along retinal layers, and GABA and glycine for the lateral inhibition; other neurotransmitters and many neuromodulators, perhaps including some neuroactive steroids [23], cooperate for the control of the visual pathway. Visual processing initiates through parallel vertical pathways that are established at the synapse between photoreceptors and bipolar cells, which convey information to retinal ganglion cells (RGCs), and at intermediate synapses with other retinal neuronal cells; glia (Müller and astrocytic cells) provide metabolic support and participate to information processing. The ganglion cells are the output neurons extending their axons to targeted brain regions throughout the optic nerve. The retinal architecture is inverted respect to the way the light enters; cone and rod photosensitive cells are located at the most external side of the retina, at the vicinity of the retinal pigment epithelium (RPE) which amplifies the light input (Fig. 1). RPE layer creates the outer blood-retinal barrier (oBRB) at the basement of the retina, with its cells forming tight junctions that limit the intercellular trafficking of molecules.

Vasculature properties of the retina are similar to those of the brain [24]. The central retinal artery branches off at the optic disc to form arterioles, which lie on the retinal surface adjacent to the vitreous humor. Branches of the arterioles assemble into networks supplying the retinal ganglion cell layer (GCL), which also receives metabolic support from vitreous humor, and the inner nuclear layer (INL). Intraretinal vascular endothelium constitutes the main component of the inner retinal-blood-barrier (iBRB; Fig.1). The lack of retinal autonomic innervation suggests that factors released locally from endothelial cells and surrounding retinal tissues are relevant for the regulation of blood flow [24,25]. Avascular areas located at the extreme retinal periphery and the outer retinal layer (ONL) containing the photoreceptors, also receive metabolic energy through the choroid, which is richly supplied from autonomic vasoactive nerves [24,26,27].

An oxygen imbalance or BRB breakdown and/or dysregulation of pro-angiogenic factors, such as the vascular endothelial growth factor (VEGF) [26,28], cause pathological neovascularization that affects retinal neuronal tissue. Angiogenic events along with neurodegenerative processes are known to be important aspects in the pathogenesis of glaucoma, diabetic retinopathy and AMD. Choroidal vessels invade the RPE and grow into the retina at the late stages of wet AMD [29,30], microvascular occlusion resulting in capillary non-perfusion and hypoxia are triggered by hyperglycemia in diabetic retinopathy [28,31], vascular risk factors (e.g. vasospasm) may be connected with absolutely (high tension) and relatively (normal tension) elevated intraocular pressure in glaucoma [32]. A current hypothesis proposes local interactions among neuronal, glial, and vascular cells for ensuring retinal blood flow at the normal function and survival. Alterations in these neurovascular interactions could evolve and contribute to diabetic retinopathy, glaucoma and AMD. Similar vascular alterations are suggested to have a part in aging, stroke, Alzheimer's disease and other neurodegenerative diseases associated with pathological neovascularization [33]. Therefore, in a functional network including endothelial cells, retinal neural cells and surrounding retinal tissues, circulating hormones and locally produced neurosteroids might guarantee retinal blood flow and prevent neurodegenerative processes.

3. Estrogen synthesis in the retina

The retina, like the brain, is a target of sex steroid hormones and a site of E2 production from cholesterol-based steroid synthesis and testosterone aromatization. The endocrine influence on visual processing was originally proposed in the late 1970s, when it was observed that susceptibility of retinal cells to light damage occurred concomitantly with sexual maturation in both male and female animals [34]. Afterward, Lanthier and Patwardhan [35,36] characterized presence and metabolism of 5-en-3β-hydroxysteroids and progesterone. In 1994, we showed the rat retinal neurosteroidogenic ability after looking at cholesterol synthesis from mevalonactone, and its transformation into pregnenolone as precursor of progestogens, corticosteroids, androgens and estrogens, using retinal explants that excluded any possible interference from circulating steroids [2]. In 2001, Salyer et al. [37], suggested that retinal thickness was affected following testosterone conversion into E2 in the RPE, having a possible implication in sexual dimorphism of visual processing in rodents and humans. Subsequent studies from our and other laboratories reported expression and activities of the key neurosteroidogenic enzymes that now allow to define the landscape of E2 synthesis starting from cholesterol or from testosterone throughout the retina [2,3,5] (see Fig. 2 for a schematic representation of the distribution of neurosteroid enzymes and E2 neurosteroidogenic pathway in the retina). Cholesterol conversion into pregnenolone and testosterone aromatization