

Hormones and Eye Diseases

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Short Communication

Precision medicine (i.e., personalized treatments) is a goal of modern biomedical research. The rationale behind this approach is that a patient's disease is always a combination of genetic and environmental factors, which make each patient almost unique, so that the objective is to develop specific treatments for the individual patient rather than for the generic disease. In this framework, hormones play an important role, since it is known that their balance is an individual signature, and their production depends on environment, age and disease.

Hormones are the main orchestrators of the body's physiology, and affect organ and tissue behavior in two ways: directly, acting through cell receptors and modulating cell function, and/or indirectly, through regulation of metabolism and the organ and tissue milieu in which cell functions are carried out.

The physiology of the eye, its health or disease state, also depends on the equilibrium of the several hormones that may affect its condition. As very often happens in biomedical research, recognition and understanding of a specific pathology is the key to the understanding of the mechanisms that regulate the normal functioning of organs and tissues. Therefore, experimental and clinical research in this field has also progressed by exploring what links exist between certain eye diseases and specific hormonal changes.

Sex Steroid Hormones

The first reported association was made by Henrik Sjogren, when in 1930 he described a correlation between hormonal changes in women and dry eye syndrome (DES) [1]. Nowadays, we do know that the imbalance of sex steroid hormones (SSH: androgens, estrogens and progesterone) have a role not only in ocular surface diseases, but in other eye pathologies, too [2]. The majority of ocular tissues (cornea, conjunctiva, lens, iris and ciliary body, retina, lacrimal gland and Meibomian glands) express SSH receptors, thus responding to a direct regulation by the presence of these hormones [2].

DES is most likely related to the imbalance of SSH that occurs with advanced age (mainly menopause), and a very

recent metanalysis has indicated that there is a difference in dry eye manifestations and symptoms between men and women, with women having dry eye signs and reporting dry eye symptoms more often than men [3].

Even though a gender bias for age-related macular degeneration (AMD) has not been clearly demonstrated, the neural retina and the retinal pigmented epithelium (RPE) directly respond to estrogens, and experimental animal model systems point to a direct involvement of estrogens in their function [2].

Glaucoma is a complex pathology, in which the dysregulation of intra-ocular pressure (IOP) and blood circulation are the main risk factors, resulting in apoptotic retinal ganglion cells (RGCs) death [4]. A sex prevalence for any type of glaucoma has not been clearly established; however, it is known that IOP values vary in females according to the menstrual cycle, thus indicating a role for SSH in the control of IOP [2].

Estrogen and androgen receptors are also found on lymphocytes and synovial macrophages, so that auto-immune and inflammatory ocular diseases (such as uveitis) appear to occur more often in women than in men [5].

Finally, increased levels of the common precursor to androgens de-hydro-epi-androsterone-sulphate (DHEA-S) and reduced levels of estrone have been found in the saliva of patients affected by keratoconus (a disease caused by thinning and relaxation of the corneal stroma) [6], suggesting a negative effect of high androgen levels and a protective effect for estrone, which might explain the higher occurrence of keratoconus observed in young men in a recent epidemiological report [7].

Insulin

Insulin is a hormone that regulates the glucose uptake and metabolism of almost every cell in the body, with the notable exception of endothelial cells [8]. The insufficient production of insulin or the peripheral resistance to its action results in hyperglycemia and diabetes. High blood glucose increases metabolism and free radical production, finally causing the toxic effects that are the hallmarks of diabetic patients. Micro and macro angiopathy and peripheral neuropathy affect ocular

tissues as well: diabetic retinopathy and macular edema are common complications of protracted hyperglycemia [9]. On the ocular surface, tear osmolarity is increased by the elevated glucose content, causing tear film instability and epithelial toxicity; neuropathy affecting cornea innervation can also result in reduced lacrimation, and an adequate supply of insulin is important for the normal proliferation and turnover of cell-surface epithelia and the functioning of the main lacrimal gland [10] as well as the Meibomian glands [11].

Thyroid Hormones

Thyroid hormones affect the eye in several ways. Hyperthyroidism causes eye globe proptosis and eyelid retraction, resulting in impaired blinking, uneven tear film distribution and high evaporation rate, which is exacerbated by the malfunctioning of the main lacrimal gland and Meibomian glands, which also depend on thyroid hormones for correct functioning and adequate tear film component production [10]. All these events may explain why DES is quite common in patients with thyroid disease [10].

Open angle glaucoma (OAG) has also been found associated with thyroid disease [12,13], most likely because the permeability of the trabecular meshwork - that governs aqueous humor outflow and thus IOP - can be decreased by an abnormal production and deposition of mucopolysaccharides that clog this normally highly permeable tissue [12].

Melatonin

A final mention goes to melatonin, a hormone mainly produced by the pineal gland (a vestigial eye), by many eye tissues and other body cells [14]. The hormonal task of melatonin (through its cognate receptors MT1, MT2 and MT3) is to regulate sleep and the circadian activities of organ functions; however, its high anti-oxidant potential also makes it a valid defense mechanism against oxidative stress. The eye is a rich source of melatonin, which plays a role in regulating its growth and development. In the retina, melatonin biosynthesis appears to be controlled by a system involving rods and the intrinsic photoreceptive retinal ganglion cells (ipRGC), and depends on at least two light-sensitive mediators: melanopsin in ipRGC and cryptochromes in the suprachiasmatic nucleus [14].

Melatonin in the retina regulates the circadian rhythms of photoreceptors' outer disk shedding and recycling by pigmented epithelial cells; moreover, because of its direct free radical scavenging activity and its ability to increase the production of endogenous anti-oxidant enzymes (GSH, GR, SOD), it is an efficient shield against the photo-oxidative damage produced in the retina by daylight, and it can efficiently attenuate the progression of AMD [15]. A similar protective effect is exerted in the crystalline lens, where it can reduce cataract formation [14].

The role of melatonin in glaucoma is more articulate. Primary open angle glaucoma (POAG) is a slowly progressing neurological disease that involves apoptotic death of RGCs,

and in which elevated IOP and vascular dysregulation are the main risk factors [4]. Melatonin is found in the aqueous humor, and melatonin receptors are expressed on retinal blood vessels, iris and ciliary body, leading to the hypothesis that they could be involved in aqueous humor production and therefore in the circadian rhythm of IOP [16]. Indeed, several experimental and clinical reports indicate that melatonin or its analogues (5-MCA-NAT and agomelatine) may significantly further decrease the IOP of glaucoma patients under multiple drug treatment with anti-glaucoma eye drops [17]. More recent clinical data have shown that melatonin at 1 mg per os can decrease IOP also in non-glaucomatous subjects (with IOP values ranging between 16 and 23 mmHg), with efficiency similar to antiglaucoma topical drugs, even though, in this case, a cooperative effect with topical medications was not observed [Pescosolido N, personal communication], most likely due to a stronger engagement of the MT3 receptors by agomelatine [17]. Furthermore, the ability of melatonin to decrease glutamate neurotoxicity and inhibit the retinal nitridergic pathway decreasing the potentially toxic retinal nitric oxide synthase (NOS) activity [16] suggests a neuroprotective efficacy of melatonin supplementation. In fact, a subcutaneous melatonin implant in a mouse model of glaucoma, which released low amounts of melatonin such that IOP was not affected, resulted in a significant neuroprotection of RGCs from apoptotic death [18]. This result implies a neuroprotective activity of melatonin that is independent of IOP regulation. Taken together, all these data suggest that melatonin eye drops could be a valid new treatment for POAG, dealing with both its IOP and neurotoxic aspects at the same time [19].

Future Direction and Recommendation

This collection of data clearly indicates the role of different hormones in controlling health and disease states of the various eye components, and suggests that hormonal balance should always be considered in the diagnostic process and the therapeutic approach to eye pathologies. Precision medicine, which is the final goal of modern therapeutic treatments, has to take into account all the aspects of a disease and its treatment, including its molecular etiology (and hormones play a role in this field), and any related therapy, if available, possibly based on the emerging rules of chronotherapy as already used for glaucoma therapy [20,21]. Of course, more studies – both experimental and clinical – are required to better define all the elements in the different ocular diseases, but we believe that the route is now clear and that data will be available soon to prepare new guidelines for a personalized treatment of a characterized disease in each patient considered as a single specific individual.

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