REVIEW

A REVIEW ON THE PHYSIOLOGICAL AND PHARMACOLOGICAL INFLUENCE OF VASCULAR TONE IN CHOROIDAL AND CONJUNCTIVAL EYE TERRITORIES

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Abstract

This review analysed the literature of the period 2006 - 2015 on the nervous and humoral control of choroidal (including the vascularization of iris and ciliary bodies) and conjunctival vascular tone. Articles referring exclusively to pathological eye and to retinal vasculature were excluded. Anatomically, choroidal and conjunctival vascular territories are two distinct territories with extensive anastomosis. In both territories active substances interfering with the adrenergic, histamine and serotonin control have been assessed. The influences in the area of the ciliary arteries/choroidal vasculature of many other vasoactive substances were studied. For substances that have been studied in both vascular territories, there were differences between the two territories. Differences in vascular reactivity are likely due to the variability in density of the different types of adrenergic, histamine and serotonin receptors, respectively.

Rezumat

Studiul și-a propus să analizeze literatura de specialitate de limbă engleză și română din perioada 2006 - 2015 privind controlul funcțional al tonusului vascular coroidian (incluzând și vascularizația iriană și a corpului ciliar) și conjunctival. Au fost excluse articolele cu referire la ochiul patologic și cele care tratează exclusiv vascularizația retiniană. Din punct de vedere anatomic, vascularizația coroidiană și conjunctivală sunt două teritorii vasculare distincte, dar intens anastomozate. În ambele teritorii au fost studiate numai substanțe active în domeniul adrenergic, serotoninergic și histaminergic. În teritoriul arterial ciliar/coroidian au fost studiate și alte substanțe vasoactive. Pentru substanțele care au fost studiate în ambele teritorii există diferențe de reactivitate vasculară între cele două teritorii, variații datorate foarte probabil diferenței de densitate a diferitelor tipuri de receptori adrenergici, histaminergici și respectiv serotoninergici.

Keywords: ciliary, choroidal, conjunctival, vascular tone

Introduction

Eye vascularization is well known by its particularities. It consists of the retinal vascular system and the uveal vascular system. Retinal circulation is a terminal vascularization without arterial anastomoses. Choroidal circulation is a non-terminal type with many arterial and arteriovenous anastomoses [19].

Ocular vascularization cannot be considered as one because of different origin from the external carotid artery and internal carotid artery respectively. It is generally considered that choroidal vasculature is derived primarily from the ophthalmic artery, a branch of the internal carotid artery. The groups of branches of the eye are represented by the following arteries: long ciliary arteries, short ciliary arteries, anterior ciliary artery, central retinal artery and muscular arteries [11]. Long posterior ciliary arteries pierce the sclera sideways of the optic nerve and splits into an upper and a lower terminal branch which anastomoses with the opposite corresponding branches and anterior ciliary arteries, forming a circle at the periphery of the iris - great arterial circle of the iris. This radial branches circle turns to the free edge of the iris where, through arterial anastomoses form the small arterial circle of iris; at this level originate the branches that supply the pupillary edge of the iris [3]. The posterior conjunctival arteries, branches from the arterial arches of the upper and lower eyelids that supply the conjunctiva, generate at the sclerocorneal *limbus* the palisades of Vogt. Anterior ciliary arteries supply blood to the bulbar conjunctiva and sclerocorneal *limbus*. They originate in the muscular branches of the ophthalmic artery. Prior to penetrate the eyeball, to 2 mm of *limbus*, ciliary arteries generate anterior conjunctival arteries, from

which anterior branches emerge and create a peri-corneal plexus. At that level perforated branches of sclera ending at the great arterial arch of iris and recurrent branches that anastomose with posterior conjunctival arteries emerge [3].

Venous vascular bed has very complex patterns which do not closely follow the ramifications of the arterial system.

Considering the differences between the two vascular territories (choroidal/extraocular and intra-ocular ciliary arteries/iris and conjunctival) there may be differences in vascular control between the two territories.

The actual review evaluated the literature of the past 10 years on the influence of choroidal (including iris and extraocular and intraocular isolated ciliary arteries) and conjunctival vasculature by various endogenous and exogenous substances.

Materials and Methods

The research of physiological and pharmacological influence on the choroidal and conjunctival vasculature through literature review, involved the use of a complex "tag" shown below, in PubMed database, including scientific papers published between 2006 - 2015 in English and Romanian, not in the category of reviews.

The used tag: *(ocular OR eye) AND (ciliary OR conjunctival OR ophthalmic OR choroid OR choroidal) AND (arteries OR capillary OR veins) AND (humans OR bovine OR dogs OR cats OR canine OR feline OR rabbits OR mice OR mouse OR rats OR murine OR rodents) AND (vasodilatation OR vasodilation OR tone OR vasoconstriction OR blood flow).*

Thus, initially 789 articles were identified. Of these, 706 were in English and one in Romanian; out of them 53 were literature review, 654 items remaining still considered.

Out of 654 articles, 653 articles have been identified to be related to the choroidal vasculature, including iris, ciliary and ophthalmic artery, and one related only to conjunctival vasculature. Out of 653 articles considered, 18 articles included references to conjunctival vasculature.

Finally, 27 articles were selected by removing the articles referring exclusively to retinal vasculature and those which analyses only the influence on vascularization of the pathological eye.

Results and Discussion

Figure 1 is showing the distribution per years of the articles originally selected, demonstrating a relatively constant interest of the scientists on the possibilities to influence the ocular vascularization.

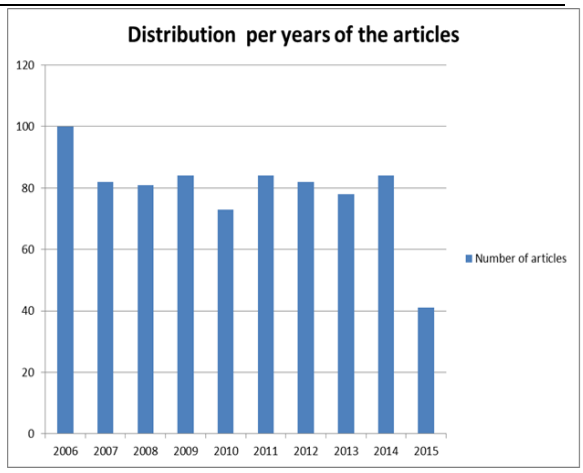

Figure 1.
Distribution *per* years of the articles originally selected

The prostaglandins are involved in the control of ocular vascular tone. In the porcine long posterior ciliary arteries and other intraocular arteries (unspecified), all experiments performed *in vitro*, prostaglandin D_2 (PGD_2) acting on DP receptors and prostaglandin E_2 (PGE_2) acting on EP_4 receptors, produced vasodilation [16]. There have not been found data, in the reviewed articles, regarding the vasodilator effects of prostaglandins on conjunctival circulation.

PGD_2 and PGE_2 caused vasoconstriction on porcine long posterior ciliary arteries, acting through thromboxane receptors (TP) [16].

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) had vasoconstrictor effect on porcine ciliary arteries and long posterior ciliary arteries *in vitro* [15].

Also, Vysniauskiene *et al.*, 2006 [26] showed that the $PGF_{2\alpha}$ produced vasoconstrictor effect on porcine ciliary arteries, effect inhibited by SQ29548 ([1S-[1α,2α(Z),3α,4α]]-7-[3-[[2-[(phenylamino)-carbonyl]-hydrazino]-methyl]-7-oxabicyclo-[2.2.1]-hept-2-yl]-5-heptenoic acid, a TP receptors antagonist) and by AL8810 (9α,15R-dihydroxy-11β-fluoro-15-(2,3-dihydro-1H-inden-2-yl)-16,17,18,19,20-pentanor-prosta-5Z,13E-dien-1-oic acid, a prostaglandin F receptor (FP) receptors antagonist). In ciliary arteries and long posterior ciliary arteries the same vasoconstrictor effect *in vitro* to travoprost and latanoprost (analogues of $PGF_{2\alpha}$) and also for U46619 (9,11-dideoxy-9α,11α-methanoepoxy-prosta-5Z,13E-dien-1-oic acid, analogue of TXA_2) acting on TP and FP receptors was shown [16, 26].

Unoprostone isopropyl, latanoprost and tafluprost ($PDF_{2\alpha}$ receptor agonists) produced vasoconstriction in mouse ciliary arteries *in vitro*. This effect was mildly affected by the cyclooxygenases inhibitors - indomethacin - and it was not influenced by the administration of L-NAME (L-N^G-Nitroarginine

methyl ester), a non-specific inhibitor of NO synthase [1].

AL-12180 ((Z)-7-[(2R,3S,4R)-2-[(E,3R)-4-(3-chloro-phenoxy)-3-hydroxybut-1-enyl]-4-hydroxyoxolan-3-yl]-hept-4-enoic acid), a PGF analogue, produced vasoconstriction in the presence of extracellular K^+ concentration of 80 mM in porcine short posterior ciliary arteries *in vitro*. Vasodilation was not recorded in any concentration, which may lead to the conclusion that AL-12180 acted only on TP receptors [22].

NO, formerly named EDRF (Endothelium-Derived Relaxing Factor), is a vasodilator factor that has as a secondary mechanism of action the transformation of GTP in cGMP [24]. According to Laspas *et al.*, 2014 [18] NO donors produce vasodilation in the mouse ophthalmic arteries *in vitro*. The same authors showed that acetylcholine had a vasodilator effect on eye arteries in mice by a NO-dependent mechanism, this effect being simulated by the administration of sodium nitroprusside and blocked by the administration of L-NAME, except for the knockout mice for the gene encoding eNOS (endothelial NO synthase).

L-NMMA (L-N^G-monomethyl Arginine) is a vasoconstrictor by nonspecific blockade of NO synthase. It produced vasoconstriction on human choroidal arteries through a NO-dependent mechanism *in vivo* [23].

H_2S donors, AP67 ((4-methoxyphenyl) pyrrolidin-1-yl phosphinodithioc acid) and AP72 ((4-methoxyphenyl)-piperidin-1-yl phosphinodithioc acid) assessed on bovine posterior ciliary arteries *in vitro*, arteries pre-contracted with phenylephrine, produced vasodilation [17].

The mechanism of vasodilation by AP 67 involves, beside H_2S, a prostaglandin component (is inhibited by flurbiprofen) also an ionotropic component by activating the ATP-sensitive potassium channel (K_{ATP}) channels (is inhibited by glibenclamide) and the involvement of NO (is inhibited by L-NAME). In case of AP72, prostaglandins are not involved but the H_2S, NO and K_{ATP} involvement was demonstrated.

On the bovine posterior ciliary arteries, considering the same method (arteries pre-contracted by phenyl-ephrine *in vitro*) Chitnis *et al.*, 2013 [4] showed that GYY4137 (p-(4-methoxyphenyl)-p-4-morpholinyl-phosphinodithioic acid), a donor of H_2S, produced vasodilation, by a mechanism involving the prostaglandin system, the administration of flurbiprofen facilitating GYY4137 vasodilator effect.

Also, the same authors showed that inhibition of H_2S by aminooxyacetic acid and propargylglycine and blocking of K_{ATP} by glibenclamide diminished the GYY4137 vasodilator effect. In addition, it was shown that the NOS inhibitor, L-NAME, did not influence the vasodilator effect of GYY4137 in the respective experiment [4].

An endothelial factor involved in blood vessels relaxation in the rat ciliary arteries territory *in vitro* is EDHF (Endothelium-derived hyperpolarizing factor). EDHF is actually a mechanism of vascular relaxation with an endothelial starting point than a substance itself, which has an independent action of blocking the pathway of prostaglandin and NO synthesis and whose action can be evidenced experimentally by administering acetylcholine in the presence of indomethacin and L-NAME on arteries precontracted with norepinephrine. The mechanism of the vasodilator effect of EDHF could consist on influencing the K_{Ca} channels sensitive to charybdotoxin (intermediate and large-conductance calcium-activated potassium channels blocker) and iberiotoxin (large-conductance calcium-activated potassium channels blocker) but not to apamin (small conductance calcium-activated potassium channels blocker) [10].

Wagenfeld *et al.*, 2013 [27] showed that in the rat eye arteries *in vitro*, the reactive oxygen species (ROS), which can be considered a part of EDHF, dilated vessels with endothelium exposed during 5 seconds (s) and 20 s. In case of vessels without endothelium, the administration of ROS for 5 s produced vasodilation while exposure to ROS for 20 s produced vasoconstriction.

Wagenfeld *et al.*, 2014 [28] tested the influence of the cells membrane potential of the vascular smooth muscle *in vitro* on the vasodilator and vasoconstrictor effects of ROS. At a resting potential of -60 mV, on ophthalmic artery in mice, ROS produced vasodilation, which was attenuated by blocking of the Na^+/K^+ ATP-dependent pump (by ouabain). At a potential of -41mV ROS caused vasoconstriction, abolished by KBR7943 (2-[4-[(4-nitrophenyl)-methoxy]-phenyl]-ethyl ester carbamimidothioic acid, mono-methanesulfonate), an ion exchanger blocker of NCX (sodium-calcium exchanger).

Adenosine dilated the bovine posterior ciliary arteries *in vitro*. ATP in the presence of a pre-treatment with alpha, beta-methylene ATP (a molecule which is a purinergic receptors antagonist, but not a specific antagonist and is slowly metabolized) also had a vasodilatory effect *in vitro*. ATP, alpha, beta-methylene ATP and uridine 5'-diphosphate produced vasoconstriction *in vitro* [30].

The administration of carbonic anhydrase inhibitors (acetazolamide, brinzolamide and dorzolamide) produced vasodilation which is dependent to NO release in porcine intraocular ciliary arteries territory *in vitro* [15]. Dorzolamide, in arteries pre-contracted with U46619 (analogue of TXA_2) showed a vasodilator effect *in vitro,* which did not involve carbonic anhydrase but involved vascular endothelium and NO [15].

Reitsamer *et al.*, 2009 [20] showed that dorzolamide increased ciliary blood flow (vasodilation) *in vivo* in rabbits without affecting blood flow of the posterior pole of the eye.

Endothelin-1 administered intravenously in humans for 30 minutes at a dose of 5 ng/kg/min caused choroidal vasoconstriction with significant decrease in choroidal blood flow *in vivo* [25].

Histamine administered to humans increased choroidal blood flow through H_1 receptors *in vivo* [29]. This effect was partially blocked by the administration of diphenhydramine (a H_1 antagonist). Dong *et al.*, 2007 [9] showed that in ciliary arteries precontracted with histamine 1 μM in rabbits *in vitro*, pyrilamine produced vasodilation by blocking H_1 receptors [9].

On the ciliary artery in rabbits, *in vitro,* Dong *et al*, 2007 [9] showed that a Ca^{2+} dependent mechanism (either by influx of Ca^{2+} in smooth muscle cells or by the release of Ca^{2+} from intracellular stores) of producing vasoconstriction was present. The authors supposed that the cause of calcium release could have as triggers: increase of the concentration of extracellular K^+, administration of doses of histamine of 1 μM, administration of phenylephrine (α_1 adrenoceptor agonist) or administration of endothelin (the most potent vasoconstrictor secreted by the endothelial cells). Levobunolol (a supposed β-adrenoceptor blocker) diminished vasoconstriction induced by any of these four substances and it was hypothesized that levobunolol acted by blocking calcium channels which were stimulated by administration of histamine 1 μM, but did not appear to influence the L-type calcium channels and did not act by β-blocking effect.

In rats iris vascular territory, *in vivo*, histamine did not significantly altered vascular tone in conjunctival administration at that level. Coman *et al.*, 2007 [5] showed that blocking of the H_1 receptor by promethazine *in vivo* did not decrease the diameter of the arterial iris vessels and histamine administered 5 minutes after promethazine had no significant effect on the diameter of the vessels. H_2 receptors blockade by ranitidine led to a significant vasoconstriction on iris vessels, antagonized by histamine administered 5 minutes after ranitidine. These data suggest that there is a histamine tonus on iris vasculature, involving H_2 receptors. All substances were instilled into the conjunctival membrane. In the area of rat conjunctival vasculature, a progressive vasodilation was produced by histamine. H_1 receptor blockade by promethazine did not modify vascular diameter and prevented vasodilation induced by histamine topically administered at 5 minutes after promethazine instillation. Pre-treatment with ranitidine did not prevent histamine vasodilation, suggesting that the dominant receptor in conjunctival vessels was the H_1 receptor.

Conjunctival administration of serotonin *in vivo*, acting on specific receptors, produced conjunctival and iridal vasoconstriction. Vasoconstrictor effect was of different intensities in the two territories, probably due to differences in density of serotonin receptors in the conjunctiva and iris [6].

Acetylcholine is not only a neurotransmitter but also a substance with non-synaptic endothelium activity. It is acting indirectly through NO, prostaglandins and so-called EDHF (which acts by K_{Ca} channels sensitive to apamin and charybdotoxin) [23]. Delaey *et al.* 2007 showed that in the bovine choroidal arteries, pre-contracted with norepinephrine, *in vitro,* the administration of acetylcholine produced a dose-dependent vasodilation up to maximal vasodilation at a 10 μM concentration. In the presence of L-NA (N^G Nitro-L-arginine, an inhibitor of NOS) vasoconstriction to norepinephrine was accentuated, but the vasodilator effect of acetylcholine in vessels pre-contracted with norepinephrine plus L-NA was unaffected. The vasodilator effect of acetylcholine was abolished in the presence of L-NA and indomethacin, in the presence of a high concentration of K^+ (30 mM) and by mechanical removal of endothelium. TEA (tetraethylammonium, a nonselective K^+ channel blocker) significantly reduced the vasodilator effect of acetylcholine. A similar effect was produced by administration of charybdotoxin (intermediate and large-conductance calcium-activated potassium channels blocker) and apamin (small conductance calcium-activated potassium channels blocker). Charybdotoxin showed *per se* vasoconstrictor effects in choroidal arteries unlike apamin, which had no effect in this vascular territory [8].

Acetylcholine produced *in vitro* vasodilation in rat ciliary arteries pre-contracted with norepinephrine, a substance that produced vasoconstriction in the respective territory by acting on α_1 receptors [10]. Also, Ziganshina *et al.*, 2012 [30] showed the vasoconstrictor effect of norepinephrine on bovine posterior ciliary arteries *in vitro*.

Epinephrine 0.1% instilled in the eye of rats produced gradual vasoconstriction in iridal territory. In the conjunctival vessels a slight vasodilation occurred initially which was followed by vasoconstriction of lower intensity than that produced at the iris vessels level. Iris vessels treated with isoprenaline 0.00002% (a β1 and β2 adrenoceptor agonist) were unaffected, unlike conjunctival vessels, among which was a significant vasodilation.

Differences in the vascular reactivity of the two vascular territories of the eye (conjunctiva and iris), when treated with vasoactive amines (epinephrine, isoprenaline), supports the idea that the β_2 adrenergic receptors are present only in the conjunctival

vessels but not at the level of the iris, while α adrenergic receptors are present in both ocular vascular territories *in vivo* [7].

Phenylephrine, an α_1 agonist, had vasoconstrictor effects on the bovine posterior ciliary arteries *in vitro* [4], on the rabbit ciliary arteries *in vitro* [9] and also produced vasoconstriction of choroidal arteries in humans *in vivo* [23, 14], Laspas *et al.*, 2014 [18] showed vasoconstrictor effect of phenylephrine on ophthalmic arteries in mice *in vitro* and Gaynes *et al.*, 2014 [13] showed vasoconstrictor effect on rabbit conjunctival arteries *in vivo*.

Isoprenaline produced vasodilation on iris and conjunctival arteries *in vivo*, suggesting that the β_2 adrenergic receptors are possible involved in this effect [7].

Arginine vasopressin acting on specific receptors caused vasoconstriction in rabbit choroidal territory *in vivo* [2].

Sildenafil and tadalafil *in vivo* increased the choroidal blood flow in humans by a cAMP-dependent mechanism [12].

On the bovine ophthalmic arteries pre-contracted by serotonin, anandamide ((5Z,8Z,11Z,14Z)-N-(2-hydroxyethyl) icosa-5,8,11,14-tetraenamide) and WIN 55212-2 ([(3R)-2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzo-xazin-6-yl]-1-naphthalenyl-methanone, mono-methanesulfonate) produced dose-dependent vasodilation *in vitro*. The mechanism of vasodilation involved the CB_1 receptors and endothelial-dependent vasodilator factors (acting through NO and the K_{Ca} channels) [21].

Table I is showing the influence of various substances in the eye vessels.

Table I

The influence of various substances in the eye vessels

Substance	Effect		Species	Reference
(route of administration)	Vasoconstriction	Vasodilation		
PGD_2 (in organ bath)	long posterior ciliary arteries *via* TP receptors	long posterior ciliary arteries *via* DP receptors	porcine*	[16]
PGE_2 (in organ bath)	long posterior ciliary arteries *via* TP receptors	long posterior ciliary arteries *via* EP_4 receptors.	porcine*	[15]
$PGF_{2\alpha}$ (in organ bath)	long posterior intraocular ciliary arteries *via* FP receptors		porcine*	[16, 26]
Travoprost (in organ bath)	ciliary arteries / long posterior intraocular ciliary arteries		porcine*	[16, 26]
Latanoprost (in organ bath)	ciliary arteries / long posterior intraocular ciliary arteries		porcine*	[16, 26]
U46619 (in organ bath)	ciliary arteries / long posterior intraocular ciliary arteries		porcine*	[16, 26]
Unoprostone isopropyl (in organ bath)	ciliary arteries		mice*	[1]
Latanoprost (in organ bath)	ciliary arteries		mice*	[1]
Tafluprost (in organ bath)	ciliary arteries		mice*	[1]
AL-12180 (in organ bath)	short posterior ciliary arteries		porcine*	[22]
NO as nitroprusside (in organ bath)		Ophthalmic arteries	mice*	[18]
L-NMMA (intravenously)	choroidal arteries		human#	[23]
AP67 (in organ bath)		posterior ciliary arteries	bovine*	[17]
AP72 (in organ bath)		posterior ciliary arteries	bovine*	[17]
GYY4137 (in organ bath)		posterior ciliary arteries	bovine*	[4]
ROS (in organ bath)		ophthalmic arteries in 5s and 20s administration	rats*	[27]
ROS (in organ bath)		denudated ophthalmic arteries in 5s administration	rats*	[27]
ROS (in organ bath)	denudated ophthalmic arteries in 20s administration.		rats*	[27]
ROS (in organ bath)		ophthalmic arteries, at resting transmembrane potential	mice*	[28]
ROS (in organ bath)	ophthalmic arteries, at -41mV transmembrane potential		mice*	[28]
Adenosine (in organ bath)		posterior ciliary arteries	bovine*	[30]
ATP+alpha, beta-methylene ATP (in organ bath)		posterior ciliary arteries	bovine*	[30]
ATP (in organ bath)	posterior ciliary arteries		bovine*	[30]
Alpha, beta-methylene ATP (in organ bath)	posterior ciliary arteries		bovine*	[30]
Uridin 5'triphosphate (in organ bath)	posterior ciliary arteries		bovine*	[30]
Acetazolamide (in organ bath)		intraocular ciliary arteries	porcine*	[15]
Brinzolamide (in organ bath)		intraocular ciliary arteries	porcine*	[15]
Dorzolamide (in organ bath)		intraocular ciliary arteries	porcine*	[15]
Dorzolamide (conjunctivally)		ciliary arteries	rabbit#	[20]
Endotelina-1 (intravenously)	choroidal arteries		human#	[25]

Histamine (intravenously)		choroidal arteries	human#	[29]
Pyrilamine (in organ bath)	ciliary arteries precontracted with histamine		rabbit*	[9]
Histamine (conjunctivally)		conjunctival arteries	rats#	[5]
Ranitidine (conjunctivally)	iridal arteries		rats#	[5]
Promethazine (conjunctivally)	prevent vasodilation on conjunctival arteries to histamine		rats#	[5]
Serotonin (conjunctivally)	iridal arteries		rats#	[6]
Serotonin (conjunctivally)	conjunctival arteries		rats#	[6]
Acetylcholine (in organ bath)		ophthalmic arteries	mice*	[18]
Acetylcholine (in organ bath)		choroidal arteries	bovine*	[8]
Acetylcholine (in organ bath)		ciliary arteries	rats*	[10]
Epinephrine (conjunctivally)	iridal arteries		rats#	[7]
Epinephrine (conjunctivally)		conjunctival arteries	rats#	[7]
Epinephrine (conjunctivally)	conjunctival arteries		rats#	[7]
Norepinephrine (in organ bath)	ciliary arteries		rats*	[10]
Norepinephrine (in organ bath)	posterior ciliary arteries		bovine*	[30]
Phenylephrine (in organ bath)	posterior ciliary arteries		bovine*	[4]
Phenylephrine (in organ bath)	ciliary arteries		rabbit*	[9]
Phenylephrine (intravenously)	choroidal arteries		human#	[14, 23]
Phenylephrine (in organ bath)	ophthalmic arteries		mice*	[18]
Phenylephrine (conjunctivally)	conjunctival arteries		rabbit#	[13]
Isoprenaline (conjunctivally)		iridal arteries	rat#	[7]
Isoprenaline (conjunctivally)		conjunctival arteries	rat#	[7]
Levobunolol hydrochloride (in organ bath)		ciliary arteries	rabbit*	[9]
Arginin vasopressin (intravenously)	choroidal arteries		rabbit#	[2]
Sildenafil (orally)		choroidal arteries	human#	[12]
Tadalafil (orally)		choroidal arteries	human#	[12]
Anandamide (in organ bath)		ophthalmic arteries	bovine*	[21]
WIN 55212-2 (in organ bath)		ophthalmic arteries	bovine*	[21]

Conclusions

The ocular vascular tone is regulated by complex systems involving both a nervous control, mainly adrenergic, and a multitude of local control systems comprising many active substances.

It's hard to conclude from the presented data whether there are differences in vasomotor control between conjunctival territory and the iridal territory, most studies being conducted on large blood vessels and even extraocular vessels. However, on the vessels belonging to the iris vasculature have been described a number of active substances such as prostaglandins, adenosine, ATP, H_2S, acetylcholine, histamine and adrenergic receptors agonists, whereas on the vessels from the conjunctival vasculature only active substances implicated in the adrenergic, histamine and serotonin control were proved to act.

The fact that some substances have been described in only one of the two territories does not necessarily mean that these substances do not act in the other territory but, simply, that substance has not been studied yet in the respective territory.

Some studies tried to highlight differences on vasomotor control between the two territories. Coman *et al.*, 2008 [7] showed, for example, that in rats, *in vivo,* vasoconstriction caused by adrenaline within the iris is more intense than that within the territory of conjunctival vessels.

On the other hand, the same author showed that, *in vivo*, isoprenaline produced a more intense vasodilation in the conjunctival territory than in the iridal territory. All this suggest that β adrenergic receptors density is higher in conjunctival vessels than at iris vessels level.

Also, regarding serotonin and histamine control, differences in the *in vivo* sensitivity between the two territories, have also been described. The histamine H_1 receptors seem to be predominant in the conjunctival territory, while H_2 receptors have a higher density within the iris.

Most probably, the above described differences are not the only differences in the vasomotor control at different eye vascular territories; further research will bring new evidence of this hypothesis.

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