REVIEW

The Role of Histamine and Serotonin in the Control of Vascular Motricity of the Anterior Ocular Segment - Review of the Literature from 1997 to 2018

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Abstract

Histamine and serotonin, besides known systemic effects, can influence vascular tone at the eye level. The review of the literature from 1997 to 2018 suggests that these ocular effects are very variable – both vasodilation and vasoconstriction. Specific agonists or antagonists acting in the histamine and serotonin domains, are probably more useful than endogenous substances as working tools for discovering the functional elements involved in regulating ocular vascular tone. Knowing that intraocular pressure regulation also depends on the vascular tone of the anterior ocular segment, some of the substances under review may be candidates for potential intraocular pressure lowering drugs.

Keywords: histamine, serotonin, eye, iris, vascular tone

Rezumat

Histamina și serotonina, pe lângă efectele sistemice cunoscute, pot influența tonusul vascular de la nivel ocular. Recenzia literaturii de specialitate din perioada 1997-2018 a arătat că aceste efecte oculare sunt foarte variabile - atât vasodilatație, cât și vasoconstricție. Substanțele care modulează la nivel de receptor aceste efecte (agoniștii și antagoniștii histaminergici și serotoninergici) sunt probabil mai utili decât substanțele endogene ca instrumente de lucru pentru descoperirea elementelor funcționale implicate în reglarea tonusului vascular ocular. Cunoscând că reglarea presiunii intraoculare depinde și de tonusul vascular al segmentului anterior ocular, unele din substanțele recenzate ar putea prezenta și efecte hipotonizante oculare.

Cuvinte cheie: histamină, serotonină, ochi, iris, tonus vascular

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INTRODUCTION

Histamine and serotonin (5-hydroxytryptamine) are two amino acid derivatives with important biological functions[1].

Histamine, an endogenous monoamine, is synthesized from the histidine and is stored in most tissues and degraded in liver by histaminase. The most important roles of histamine are: mediation of type I allergic reactions, stimulation of stomach secretion of hydrochloric acid and pepsin (as autacoid), and functioning as a neurotransmitter (especially in the central nervous system)[2]. Regarding the vascular effects of histamine in non-ocular territories, there have not been many published literature reviews, for example, there are data reviewed for pulmonary artery[3], brain territory[4], but these data are not recent.

Serotonin (5-HT), synthesized from the tryptophan, exhibits vascular effects, which began to be studied a few years after its discovery (the "vasoconstriction-producing serum substance" described and identified as 5-hydroxytryptamine by Rapport in 1948)[5]. Several reviews about the cardiovascular effects of serotonin[6] have been published.

AIM

This paper aims to evaluate the influence of histamine, serotonin and related substances acting on histamine and serotonin receptors upon anterior ocular vascularisation by studying the literature from 1997-2018.

For the purpose of explaining the working method of the reviewed scientific articles, it is necessary to present a brief introduction to the vascular anatomy of the anterior ocular segment.

Anatomical data on anterior eye segment vascularization

Choroid vascularization includes ophthalmic artery branches: two long posterior ciliary arteries (LPCA) and a variable number of two to four short ciliary arteries originated either in the ophthalmic artery or LPCA. The iris and the ciliary body are considered to be a unitary one because they have the same embryological origin and the same arterial vasculature, mainly provided by the LPCA. Anterior ciliary arteries are described in humans, but are absent in some mammalian species (e.g., in the rat). At the level of the ocular equator, the two LPCAs pass from the supra-corodial space into the choroid, from where it continues to the ciliary body, at which level each vessel divides dichotomically - a dorso-anterior and a ventro-anterior branch to form the great arterial artery of the iris[7].

MATERIALS AND METHODS

We used the pubmed.com electronic platform of the National Library of Medicine using a non-restrictive tag: "(histamine OR serotonine OR 5-HT OR 5-hydroxytryptamine) AND (eye OR eye) AND (vessels OR arteries OR veins)". The "Date publication" filter was chosen between 1997/01/01 and 2018/12/31. A total of 65 articles resulted at the search performed on 2018/02/01. It is noted that the interest in this field is slightly decreasing compared to the period 1984-2012 (see Figure 1). Of these, 20 articles of interest were selected by reading the abstracts (no articles referring strictly on retinal circulation were selected).

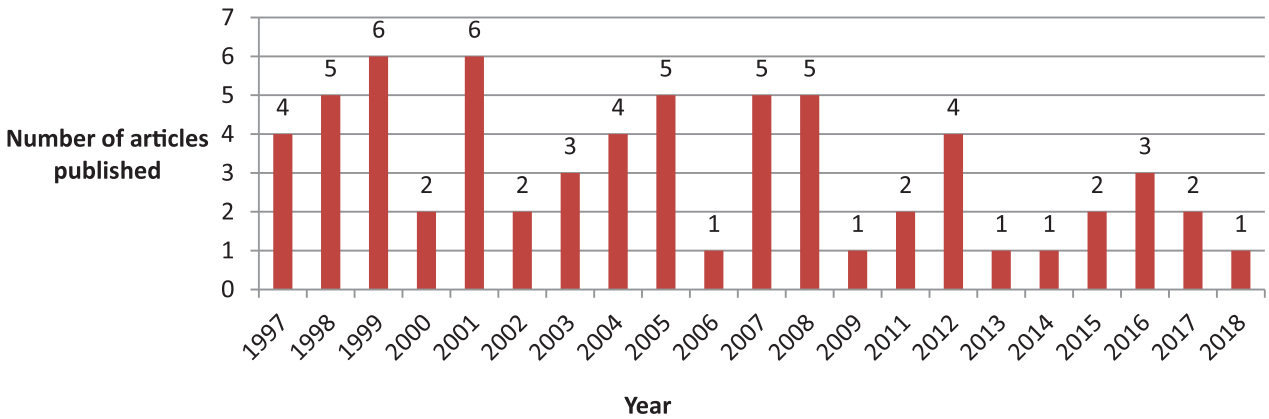

Figure 1. Distribution of the articles in the field of histamine, serotonin and eye anterior segment published in the period 1997-2018.

Table 1.

Substances	VD (VC antagonized)	VC (VD antagonized)	No effect	Sperciés, teritory, method	References
Histamine		+		*in vitro,* normal rabbit, PC arteries in the presence or absence of endothelium	11
L-NMMA[a] + Histamine		+		*in vivo* (i.v. administration), healthy men, choroid vessels	12
Histamine		+		*in vitro,* normal rabbit, PC arteries	13
Histamine		+		*in vitro,* normal rabbit, PC arteries	14
Histamine	+			*in vivo* (i.v. administration), in healthy men, choroid vessels	15
Histamine		+*		*in vitro,* normal porcine, PC arteries	16
Histamine	+			*in vivo* (i.v. administration), healthy men, choroid vessels	17
Histamine + cimetidine	+ **			*in vivo* (i.v. administration), healthy men, choroid vessels	17
Histamine	+			*in vivo* (i.v. administration), healthy men, choroid vessels	18
Histamine + diphenhydramine		+		*in vivo* (i.v. administration), healthy men, choroid vessels	18
Histamine		+		*in vitro,* normal rabbit, ciliary arteries (not specified)	19
Histamine + pyrilamine	+			*in vitro,* normal rabbit, ciliary arteries (not specified)	19
Histamine + cimetidine		+		*in vitro,* normal rabbit, ciliary arteries (not specified)	19
Histamine + Low Calcium	+ ***			*in vitro,* normal rabbit, ciliary arteries (not specified)	19
Histamine + cimetidine		+		*in vitro,* normal porcine, ciliary arteries (not specified)	20
Histamine + cimetidine + mepyramine	+			*in vitro,* normal porcine, ciliary arteries (not specified)	20
Histamine	+			*in vivo* (topical administration), normal rats, iris vessels	21
Promethazine + Histamine			+	*in vivo* (topical administration), normal rats, iris vessels	21
Ranitidine + Histamine	+			*in vivo* (topical administration), normal rats, iris vessels	21
Promethazine			+	*in vivo* (topical administration), normal rats, iris vessels	21
Ranitidine		+		*in vivo* (topical administration), normal rats, iris vessels	21
Histamine	+			*in vivo* (topical administration), normal rats, conjunctival vessels	21
Promethazine + Histamine			+	*in vivo* (topical administration), normal rats, conjunctival vessels	21
Ranitidine + Histamine	+			*in vivo* (topical administration), normal rats, conjunctival vessels	21
Promethazine			+	*in vivo* (topical administration), normal rats, conjunctival vessels	21
Ranitidine			+	*in vivo* (topical administration), normal rats, conjunctival vessels	21
Histamine (low Ca)		+		*in vitro,* normal rabbit, PC arteries	22
Histamine (low Ca) + high K		+		*in vitro,* normal rabbit, PC arteries	22
Histamine	+			*in vivo* (topical administration), normal Guinea pigs, conjunctival vessels	23
Histamine (low Ca)		+		*in vitro,* normal rabbit, PC arteries	24
Histamine (low Ca) + high K		+		*in vitro,* normal rabbit, PC arteries	24
Histamine		+		*in vitro,* normal bovine, PC arteries	25
5-HT		+		*in vitro,* normal bovine, PC both endothelium intact and denuded arteries	26
5-HT + L-NNAb		+ ****		*in vitro,* normal bovine, PC both endothelium intact and denuded arteries	26
Ketanserin	+			*in vivo* (topical administration), healthy men, choroid vessels	27
5-HT		+		*in vitro,* normal porcine, ciliary arteries (not specified)	28
melatonin + 5 - HT	+			*in vitro,* normal porcine, ciliary arteries(not specified)	28
5-HT		+		*in vitro,* normal porcine, ciliary arteries (not specified)	20

Table 1. *continuare*

Substances	VD (VC antagonized)	VC (VD antagonized)	No effect	Sperciess, teritory, method	References
5-HT + ketanserin	+			*in vitro,* normal porcine, ciliary arteries (not specified)	20
Sumatriptan			+	*in vitro,* normal porcine, ciliary arteries (not specified)	20
Sumatriptan + BRL15572[c]			+	*in vitro,* normal porcine, ciliary arteries (not specified)	20
Sumatriptan + SB224289[d]			+	*in vitro,* normal porcine, ciliary arteries (not specified)	20
5-HT		+		*in vivo* (topical administration),normal rats, iris and conjunctival vessels	29
MK-212[e]		+		*in vitro,* normal bovine, PC arteries	30
BW723C86[f]		+		*in vitro,* normal bovine, PC arteries	30
R-DOIg		+		*in vitro,* normal bovine, PC arteries	30
5-HT, *****		+		*in vitro,* normal bovine, PC arteries	30
8-OH-DPAT[h]			+	*in vitro,* normal bovine, PC arteries	30
quipazine			+	*in vitro,* normal bovine, PC arteries	30
BW723C86 + RS-127445[i]			+	*in vitro,* normal bovine, PC arteries	30
BW723C86 + M-100907[j]			+	*in vitro,* normal bovine, PC arteries	30
MK-212 + RS- 102221[k]			+	*in vitro,* normal bovine, PC arteries	30

VC=vasoconstriction, VD=vasodilation, PC=posterior ciliary⋆in retinal arterioles the effect was opposite –VD, **cimetidine had no effect, ***histamine provokes contractions using Ca2+ that enters through voltage-dependent and receptor-dependent Ca2+ channels, as well as from intracellular Ca2+ stores, ****L-NNA did not influenced the vasoconstrictor effect of 5-HT, ***** α-methyl-5-HT; 5-methoxy-α-5-methyl-5-HT; cabergoline; 5-methoxy-dimethyl-tryptamine; 2-methyl-5-HT; Tryptamine – nonselective 5-HT receptor ligands were also studied having vasoconstrictor effects.

[a] L-NMMA = acetic acid; (2S)-2-amino-5-[(N'-methylcarbamimidoyl)amino]pentanoic acid (N(omega)-Monomethyl-L-Arginine), [b] L-NNA = N omega-Nitro-L-Arginine, [c] BRL 15572 = 3-(4-(3-chlorophenyl)piperazin-1-yl)-1,1-diphenyl-2-propanol, [d] SB224289 = [4-[2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]phenyl]-(1'-methylspiro[6,7-dihydro-2H-furo[2,3-f] indole-3,4'-piperidine]-5-yl)methanone, [e] MK-212 = 2-chloro-6-piperazin-1-ylpyrazine, [f] BW723C86 = 1-[5-(thiophen-2-ylmethoxy)-1H-indol-3-yl]propan-2-amine;hydrochloride, [g] R-DOI = (2R)-1-(4-iodo-2,5-dimethoxyphenyl)propan-2-amine, [h] 8-OH-DPAT = 7-(dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol, i RS-127445 = 4-(4-fluoronaphthalen-1-yl)-6-propan-2-ylpyrimidin-2-amine, [j] M-100907 = (R)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methanol (Volinanserin), [k] RS- 102221= N-[5-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5] decan-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-4-(trifluoromethyl)benzenesulfonamide.

Observations: L-NMMA and L-NNA are NO synthase inhibitors, for the specific pharmacological effects for the other substances, see Table 2.

RESULTS

Of the 20 selected articles, 14 refer only to the histamine domain, 5 refers to the serotonin domain and one article refers to both domains. In addition, we have considered in Discussion section three literature reviews (Buckley, Hadoke, & O'Brien, 1997, Sharif, 2010, Zugravu et al., 2016)[8,9,10].

The results are presented in Table 1.

DISCUSSION

The histamine system

According to IUPHAR[31], the histamine receptors described so far are of four types: H_1, H_2, H_3, H_4. H_1 receptors are widely distributed in the body, including the eye and the eye surface[32,33], under basal or pathological conditions, such as chronic ocular allergies. H_2 receptors are described mainly in the gastric mucosa, but also in vessels, including ocular blood vessels, causing VD[32,34]. H_3 receptors are found in the brain and the nasal mucosa[34-36]. H_4 receptors are expressed on mast cells and immune system cells, play a role in chemotaxis and together with H_2 receptors, control IL-16 release[37,33].

In the following, according to IUPHAR, we will present histamine receptor-associated intracellular signaling systems.

H_1 receptors are coupled with the G_q/G_{11} protein family, having as primary mechanism of action the stimulation of adenylate cyclase through Gβγ subunit of Gq protein, and as secondary transduction mechanism, the activation of phospholipase C (PLC)[38].

H_2 receptors use the G_q/G_{11} family of proteins as the primary mechanism of transduction, with sequential activation of PLC, and as a secondary mechanism, the G_s protein family which stimulates adenylate cyclase[38].

H_3 receptors are coupled to the G_i/G_o protein family, with the subsequent adenylate cyclase inhibition. By the year 2017, H_3 receptors have not been described in mammalian ocular structures[38].

H_4 receptors are coupled to the G_i/G_o protein family with consequent activation of PLC[38].

Table 2.

Domain	Agonist/antagonist receptors	Substances	Possible intracellular signalling	*In vitro*	*In vivo*
H	Histamine			VC	VD
	H_1 blockers	promethazine, pyrilamine, diphenhydramine	Decrease Ca^{2+} - Gq dependent, Decrease NO		No effect or VC
	H_2 blockers	cimetidine, ranitidine	Decrease cAMP, Decrease NO		VC
	H_1 + H_2 blockers		Decrease cAMP/Ca2+ signaling	VD	
5-HT	Serotonin			VC	VD (unpublished results)
	5-HT_{1A} agonist	8-Hydroxy DPAT	Decrease cAMP	No effect	
	5-HT_{2A} agonist	R-DOI	Increase Ca^{2+} - Gq dependent	VC	
	5-$HT_{2A/2B}$ agonis	BW -723C86	Increase Ca^{2+} - Gq dependent	VC	
	5-HT_{2C} agonist	MK-212	Increase Ca^{2+} - Gq dependent	VC	
	5-HT_3 agonist	quipazine	Increase $Na^+ = K^+ > Ca^{2+}$ transmembranary ion flux	No effect	
	5-$HT_{1B/1D}$ antagonist	Sumatriptan	Increase cAMP	No effect	
	5-HT_{2A} antagonists	M-100907	Decrease Ca^{2+} Gq dependent	Blocked VC induced by 5-$HT_{2A/2B}$ agonist-induced	
		Ketanserin	?		VD
	5-HT_{2B} antagonists	RS-127445	Decrease Ca^{2+} - Gq dependent	Blocked VC induced by 5-$HT_{2A/2B}$ agonist	

The localization of specific H_1, H_2, H_3 and H_4 receptors in human and mammalian ocular structures is still elusive[39].

According to some clinical observations, intraocular pressure (IOP) could be increased by H_2 blockers (cimetidine and ranitidine)[40,41], data that was not found in the summary of each medicine product characteristics[42,43]. It is very difficult to demonstrate the involvement of H_1 receptors in the setting of IOP in clinical trials, as most H_1 inverse agonists or antagonists also exhibit anticholinergic actions[44].

Regarding earlier research conducted before 1997, in the data reviewed by Buckley et al.,1997, histamine was not studied in the PC arteries[8]. In one of the studies, histamine produced VD in the retinal arteries with intact endothelial artery, *in vitro*. In bovine eyes, VD is probably dependent on NO and cyclooxygenase (COX). In human eyes, the VD component of the ophthalmic artery is H_2-mediated and independent of vascular endothelium. In canide, VD is partially dependent of H_2 receptors on vascular smooth muscle fibers, but is not (probably) dependent on endothelium. In bovine eyes and cat eyes, the histamine response is VC[8,12].

In rat eyes, *in vivo,* histamine produced a statistically insignificant VD of the irian arteries and antagonized VC induced by ranitidine[21]. *In vivo,* histamine produced VD of the conjunctival territory in Guinea pig eyes and at the level of choroidal vessels in humans[23,12]. In human eyes, histamine induced VD in the choroidal territory is NO dependent (VD is significantly attenuated by concomitant administration of L-NMMA). In the porcine ciliary arteries, *in vitro,* blocking H_1 produces VD[20].

H_1 blockers have no effect on vascular size in rat iris[21].

H_2 blockers have a VC effect in the rat *in vivo*[21], but not in humans, in the choroidal territory[17].

The serotonin system

There are 7 types of serotonin receptors, of which 5-HT_3 are ion channels, and 5-HT_{1-2} and 5-HT_{4-7} are coupled to G proteins[45]. Reviews of types and receptor subtypes have recently been published[46,47].

The most common types and subtypes of the anterior segment of the eye are 5-HT_{1A}, 5-HT_{2A-2C}, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_7 [9,48]. 5-HT_6 receptors were detected only at irian level, but are poorly expressed[9,48].

ROLES:

Serotonin receptors and their intracellular signal transduction mechanisms are very complex. The importance of each mechanism is difficult to assess without the

use of agonists or antagonists with specific action on these receptor types or subtypes. The review published by Sharif et al., 2010 presents the intraocular pressure lowering effect of at least 20 substances in Cynomolgus monkeys. 5-HT_6 antagonists have shown intraocular pressure lowering effect, which may lead us to the conclusion that there are off-target effects of these very specific agonists or antagonists. The most obvious data on ocular hypotensive effect were obtained for 5-HT_{2A} agonists or 5-HT_{2A}/5-HT_{2C} mixt agonists[9].

Very old research on feline and equine animal model showed that 5-HT produces contraction of the iris sphincter muscle and relaxation of the iris radius muscle[49].

EFFECTS AND LOCATION:

5-HT_{1A} receptors are mainly coupled to the G_i/G_o protein family[50] and are involved in the antioxidant protection of the retinal pigment epithelium[51] and the function of the iris sphincter muscle[52,49].

5-HT_{2A} receptors are mainly coupled with the G_q/G_{11} protein family[53]. The same type of intracellular coupling exists for 5-HT_{2B} and 5HT_{2C} receptors. There are some studies in animals and humans (Phase II studies) with 5-HT_{2A} agonists for the treatment of glaucoma[9,48]. They are found mostly at the trabecular meshwork. 5-HT_{2B} and 5-HT_{2C} receptors are also involved in lowering IOP, with the remark that the 5-HT_{2C} receptors are not constantly expressed in the ciliary body. They are especially found in the central nervous system.

5-HT_3 receptors are ligand-dependent ion channels with the following ionic conductivity: $Na^+ = K^+ > Ca^{2+}$ [54]. 5-HT_3 receptors are expressed inconstantly in the human ciliary body and probably play a minor role in regulating intraocular pressure[9].

5-HT_4 receptors are found in the ciliary body, choroida, conjunctiva and inconstantly in iris.

5-HT_5 receptors are found in the ciliary body and iris.

5-HT_7 receptors were highlighted in the ciliary body, iris and conjunctiva[48].

Earlier research from 1997 have shown that in vitro, 5-HT produces a vasoconstrictor effect of the ciliary and/or ophthalmic arteries of various species: canines, felines, bovines, monkeys and humans[8]. Our *in vivo* research on rats showed that the 2.5 mM concentration of 5-HT topically applied to the eye surface, has an important VD effect in the iris arteries (our unpublished results).

Buckley et al.[26] studied endothelial denuded bovine vessels, in which 5-HT produced vasoconstriction. *In vitro,* vasoconstrictive effects of 5-HT have been highlighted in the literature since 1997. In ciliary arteries obtained from bovine and pigs eyes, various researchers have demonstrated that 5-HT administration, as well as specific or selective 5-HT_2 receptor subtypes agonists, produced vasoconstriction. A recent article, published by Njie-Mbye et al., 2018, showed that 5-HT_2 agonists (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) produced VC that can be antagonized by 5-HT_2 receptor blockers. 5-HT_1 receptor agonists did not produce vasoconstrictor effect *in vitro*[30].

A list of effects obtained by *in vitro* or *in vivo* administration of the substances from the histamine and serotonin systems are presented in Table 2.

CONCLUSIONS

It is noted that administration of histamine or serotonin in different ways (topical - on the ocular surface, intravenously or in organ bath), may have opposite effects and is highly dependent on species and experimental conditions. Specific 5-HT_2 receptor agonists are probably vasoconstrictor substances, and 5-HT_2 blockade produces VD that could be a new way of lowering IOP. Regarding the histamine domain, it is difficult to find substances that cause VD or even decrease IOP.

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