The Effect of Vasopressin on Choroidal Blood Flow, Intraocular Pressure, and Orbital Venous Pressure in Rabbits

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PURPOSE. To investigate the effects of arginine-vasopressin (AVP) on intraocular pressure (IOP), orbital venous pressure (OVP), and choroidal blood flow (ChorBF) regulation in anesthetized rabbits.

METHODS. Mean arterial pressure (MAP), IOP, and OVP were measured by direct cannulation of the central ear artery, the vitreous, and the orbital venous sinus, respectively. Laser Doppler flowmetry was used to record ChorBF. To change the perfusion pressure (PP), MAP was manipulated mechanically with occluders around the aorta and vena cava. In the first group of animals ($n = 11$) the dose-response relationship was measured. In the second group of animals ($n = 8$) pressure-flow relationships were determined at baseline and in response to intravenous application of a low (0.08 ng/kg/min) and a high (1.33 ng/kg/min) infusion rate of AVP.

RESULTS. AVP caused a dose-dependent increase of MAP and choroidal vascular resistance (ChorR), whereas IOP, OVP, ChorBF, and heart rate (HR) were decreased. In contrast to the high infusion rate, the low infusion rate of AVP had no effect on baseline ChorBF. However, the pressure-flow relationship was shifted downward significantly by both infusion rates at PP below baseline.

CONCLUSIONS. AVP reduces IOP and OVP significantly and is a potent vasoconstrictor in the choroidal vascular bed. In the choroid, the effect of AVP is not only dose-dependent, but also PP-dependent, which is indicated by the reduced perfusion relative to control with low-dosed AVP at low PP. (*Invest Ophthalmol Vis Sci.* 2011;52:7134–7140) DOI: 10.1167/iovs.11-7791

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Choroidal blood flow (ChorBF) is known to be influenced by a broad variety of vasoactive substances of endothelial, humoral, and neurohumoral origin. For example, acetylcholine, bradykinin, histamine, dopamine, and nitric oxide cause vasodilatation, whereas angiotensin-II, endothelin-1, prostaglandin-H₂, and epinephrine induce vasoconstriction of ocular vessels.^{1–4}

Vasopressin, synonymously called antidiuretic hormone, is also a well-known vasoconstrictor that acts in a dose-dependent manner in many vascular beds (e.g., heart, muscle, lungs, pancreas, and spleen).⁵ The response of vessels to vasopressin is not only dose-dependent but also different in various vascular beds,⁶ with the most pronounced effects in the splanchnic circulation, skin, and arteriovenous shunts.⁵ In vitro investigations on isolated rabbit arterial segments revealed a vasopressin-induced constriction of vessels.⁶ Interestingly, in some vascular beds, very low concentrations of vasopressin caused vasodilatation,⁷ an effect that has also been observed in isolated ciliary arteries.⁸ Previous investigations on the effect of vasopressin receptor antagonists on nonselective nitric oxide synthase blockage and on pituitary adenylate cyclase-activating polypeptide application have been published by this group (Kiel JW) and by others.^{1,9} However, these studies^{1,9} rather investigated the effect of vasopressin antagonists on the action of other drugs than the role of the vasopressin system in the regulation of choroidal vascular resistance (ChorR) and ChorBF.

Apart from being a potent vasoactive substance, vasopressin is also essential for osmoregulation and for the maintenance of water homeostasis. Considering the effect of vasopressin on fluid balance, it is reasonable to assume that it might also be involved in the regulation of intraocular pressure (IOP) homeostasis. Numerous studies have been performed to elucidate the effect of vasopressin on IOP. Experimental approaches include intraocular (vitreous or anterior chamber),¹⁰ intracerebroventricular (third ventricle),^{10,11} topical,^{12,13} subconjunctival,¹² and intravenous^{10,12} application of vasopressin. Depending on the type of application, different results were obtained. Even though the results are ambiguous, it seems feasible that vasopressin is important for hemodynamic and hydrodynamic processes in ocular tissues.

The present study was performed to investigate the acute effect of intravenously applied arginine-vasopressin (AVP) on ChorBF, IOP, and orbital venous pressure (OVP), including the systemic parameters mean arterial pressure (MAP) and heart rate (HR), in an acute rabbit model.

METHODS

All animal procedures were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the ARVO

Statement for the Use of Animals in Ophthalmic and Vision Research. At the end of the experiment, all animals were euthanatized with an overdose of anesthetic without ever regaining consciousness.

Animal Preparation

New Zealand albino rabbits (weight range, 2–3 kg; $n = 19$) of both sexes were housed for 1 to 3 weeks in a vivarium with food and water available ad libitum before the experiments. They were anesthetized with pentobarbital sodium (30 mg/kg, administered intravenously, supplemented as needed; Fagron GmbH, Barsbüttel, Germany). To eliminate eye movement, the animals were paralyzed with gallamine triethiodide (1 mg/kg, intravenously; Sigma-Aldrich, St. Louis, MO). All parameters were measured continuously and simultaneously.

The animals were intubated through a tracheotomy and artificially respired with room air by an advanced safety ventilator (Harvard Inspira; Harvard Apparatus, Holliston, MA). Expired PCO_2 was monitored (Capnograph V90041; SurgiVet, Waukesha, WI) and maintained at 40 to 45 mm Hg. A heating pad was used to maintain normal body temperature (38°C–39°C). A flexible tube was inserted into the femoral artery for taking blood samples. The measurement of ocular parameters was performed as previously published by Reitsamer and Kiel¹⁴ and is just briefly described.

Measurements of MAP, IOP, OVP, and ChorBF

To estimate MAP at the eye level and to ensure the adequacy of anesthesia, a catheter was inserted into the right ear artery and was connected to a pressure transducer positioned at the same height above the heart as the eye. For manipulating MAP within a specified range, hydraulic occluders were placed around the descending thoracic aorta and the inferior caval vein through a right thoracotomy. To avoid influences of humoral factors due to pressure manipulations, the occlusions were kept short to allow the model to recover for 15 minutes between each pair of occlusions. All intravenous injections were given through cannulas placed in the marginal ear veins.

To measure IOP, a 23-gauge cannula connected to a second pressure transducer was advanced through the pars plana into the vitreous cavity of the right eye. To measure OVP with a third pressure transducer, the orbital venous sinus was cannulated with a 23-gauge needle inserted through the posterior supraorbital foramen. Perfusion pressure (PP) was calculated as MAP minus IOP.

ChorBF was measured by laser Doppler flowmetry (Periflux 4001 Maser; Perimed, Stockholm, Sweden) at a wavelength of 635 nm. The probe (PF 403; Perimed) was advanced through the pars plana and the vitreous to the posterior pole of the eye with a micromanipulator. Given that the rabbit retina is primarily avascular and the probe was directed away from the few existing retinal vessels, in this preparation the flux signal originated solely from the choroid.¹⁵ ChorR was calculated as the flux value in arbitrary perfusion units (P.U.) divided by PP (mm Hg). Before any manipulations and cannulations were made, the right eye was anesthetized topically with lidocaine hydrochloride (Xyllocaine 1%; AstraZeneca, London, UK) to avoid the ocular trauma response. Furthermore, care was taken not to disturb the cornea, lens, and anterior chamber.^{16–18}

Measurement of Plasma AVP

To determine AVP plasma levels, 2 mL blood was withdrawn into a chilled EDTA-tube at baseline and at each infusion rate. Samples were centrifuged immediately for 10 minutes. The separated plasma was frozen and stored at -20°C until AVP determination. A commercially available radioimmunoassay (Arginine Vasopressin RIA DSL-1800i; Diagnostic Systems Laboratories, Webster, TX) was used to detect AVP levels in plasma.

Experimental Protocols

Two separate groups were used for this study. The first group ($n = 11$) was used to acquire the dose-response relationship for AVP (arg-

vasopressin acetate [Sigma Aldrich] dissolved in 0.9% saline solution). The infusion rate (ng/kg/min) was increased gradually over time, and blood samples were taken from the femoral artery to determine the AVP concentration in the blood. To avoid changes in blood volume, all withdrawn blood volumes were replaced by sterile isotonic saline. Blood draws were taken at baseline (to estimate the endogenous level of AVP) and at each infusion rate under steady state conditions. Applied infusion rates were 0.04, 0.08, 0.16, 0.33, 0.67, 1.33, 2.67, and 5.33 ng/kg/min. Figure 1 shows the correlation between infusion rates at steady state and plasma levels of AVP.

The second group of animals ($n = 8$) was used to determine the effect of AVP on blood flow regulation in the choroidal vascular bed by measuring choroidal pressure-flow relationships in response to mechanical manipulations of ocular PP. Based on the effects of increasing infusion rates of AVP on ChorBF at baseline, two different infusion rates of AVP were chosen for measurements of the pressure-flow relationships. The first (low) infusion rate (0.08 ng/kg/min) did not change baseline ChorBF. The second (high) infusion rate (1.33 ng/kg/min) caused a significant reduction of baseline ChorBF. To determine the effect of changes in ocular PP on the regulatory response of the choroidal vascular system, mechanical manipulations of blood pressure were performed by an aortal and a caval occluder. Occlusions were conducted at baseline conditions, at the low infusion rate and at the high infusion rate. Figure 2 shows a representative tracing of the experimental protocol.

Statistical Analysis

All measured parameters were recorded at 100 samples per second with a digital data acquisition system (PowerLab; ADInstruments, Grand Junction, CO). ChorR was calculated as the ratio between PP (mm Hg) and ChorBF (P.U.).

The dose-response relationship was evaluated by one-way repeated-measures analysis of variance (RM ANOVA) followed by post hoc *t*-tests with Bonferroni correction. The measured variables for pressure-flow relationships were averaged in 5 mm Hg bins of PP. To identify differences in pressure-flow curves, RM ANOVA with two within factors (treatment and PP), followed by paired contrasts using the Bonferroni adjustment (SigmaPlot 11.0; Systat Software Inc., Chicago, IL), was performed to assess the effect of AVP on the pressure-flow relationship. $P < 0.05$ was regarded as significant. All results are expressed as mean $\pm$ SEM.

FIGURE 1. Relationship between plasma AVP and AVP infusion rate. The plot shows a good correlation between intravenously applied infusion rates and plasma levels of AVP. Results are expressed as mean $\pm$ SEM.

FIGURE 2. Representative tracing for evaluation of pressure-flow relationship. Three series of aortic and caval occlusions are shown. The first occlusions were performed at control conditions, the second occlusions during application of 0.08 ng/kg/min AVP, and the third occlusions during application of 1.33 ng/kg/min AVP (arrows, baseline changes). For every infusion rate equilibration of measured parameters was awaited before pressure manipulation.

RESULTS

Effect of AVP on Baseline Parameters

Intravenously applied AVP caused dose-dependent effects on all measured parameters. While MAP and ChorR increased, IOP, OVP, ChorBF, and HR decreased. Table 1 summarizes the effects of three AVP infusion rates (low, 0.08 ng/kg/min; medium, 0.67 ng/kg/min; high, 1.33 ng/kg/min) on the measured parameters. Hemodynamically and hydrodynamically relevant data show that the low infusion rate of AVP caused a $12.6\% \pm 1.6\%$ increase in MAP ($P < 0.001$) that rose with higher infusion rates up to $16.3\% \pm 1.6\%$, reaching a plateau. The effect was accompanied by a significant decrease of HR at the high infusion rate ($P = 0.002$). At this infusion rate, IOP was reduced by $14.4\% \pm 2.1\%$ ($P < 0.001$). High relative changes were measured for OVP ($-53.8\% \pm 6.9\%$; $P < 0.001$) and ChorR ($95.7\% \pm 24.1\%$; $P < 0.001$). However, the absolute values of OVP changes were comparatively small. The decreases in ChorBF at the medium and high infusions rates were $-16.2\% \pm 4.9\%$ ($P = 0.025$) and $-28.7\% \pm 6.7\%$ ($P = 0.002$), respectively. In Figure 3, the dose-response relationships for MAP, HR, IOP, OVP, ChorBF, and ChorR plotted against the detected AVP levels in plasma are illustrated. All parameters in Figure 3 show a clear relationship between AVP concentration in the plasma and its effect.

Effect of AVP on Choroidal Pressure-Flow Relationships

The choroidal pressure-flow relationship was significantly shifted downward by both the low and the high infusion rate

of AVP, indicating a significant increase in ChorR. Whereas at the high infusion rate of AVP vasoconstriction becomes apparent over the whole range of PP, at the low infusion rate significant vasoconstriction occurs only at PP below 45 mm Hg (Fig. 4).

DISCUSSION

Impairment of ocular blood flow is involved in the pathogenesis of numerous ocular diseases, among them diabetic retinopathy, glaucoma, and macular degeneration.^{4,19–21} ChorBF is the only provider of nutrients and oxygen to the foveal retina, and it is known to be modulated by a great variety of pharmacologic agents. Current research on ChorBF is focused on the detection of new vasoactive modulators and the clarification of the pharmacologic aspects of blood flow homeostasis in this important vascular bed of the eye. The present study sought to investigate the effect of the AVP on ChorBF, ChorBF regulation, IOP, OVP, and systemic variables.

Arginine-Vasopressin

Vasopressin, or its most common mammalian isoform AVP, acts as a hormone, neurotransmitter, and neuromodulator. AVP is a nonapeptide synthesized mainly in the perikarya of magnocellular neurons of the supraoptic nucleus and the paraventricular nucleus. AVP secretion is induced by various stimuli as increased plasma osmolality, decreased arterial pressure, and reduced cardiac filling (e.g., decreased blood volume due to hemorrhage).²² Osmoreceptors in the CNS located in the anterior region of the hypothalamus and in the mesenteric and

TABLE 1. Dose-Response Relationship of Systemic and Ocular Parameters during Increasing Infusion Rates of AVP. Although ChorBF Was Not Altered During 0.08 ng/kg/min AVP Infusion, Significant Changes Occurred at 0.67 and 1.33 ng/kg/min AVP, Respectively

Parameter	Control	AVP (0.08 ng/kg/min)	Change (%)	P	n
MAP, mm Hg	64.0 ± 0.3	72.1 ± 1.1	12.6 ± 1.6	<0.001	11
IOP, mm Hg	12.3 ± 0.9	13.0 ± 1.1	4.7 ± 2.2	NS	11
OVP, mm Hg	2.0 ± 0.2	1.8 ± 0.2	−9.5 ± 1.9	NS	11
ChorBF, P.U.	406.5 ± 19.7	410.4 ± 18.5	1.2 ± 1.2	NS	11
PP, mm Hg	51.7 ± 1.0	59.1 ± 1.4	14.3 ± 1.8	<0.001	11
ChorR, mm Hg/P.U.	0.13 ± 0.01	0.15 ± 0.01	13.1 ± 1.9	NS	11
HR, bpm	194.1 ± 11.1	190.7 ± 16.5	−4.4 ± 5.6	NS	11

Parameter	Control	AVP (0.67 ng/kg/min)	Change (%)	P	n
MAP, mm Hg	64.0 ± 0.3	74.4 ± 1.0	16.3 ± 1.6	<0.001	11
IOP, mm Hg	12.3 ± 0.9	11.5 ± 1.0	−7.1 ± 2.9	NS	11
OVP, mm Hg	2.0 ± 0.2	1.1 ± 0.2	−45.5 ± 6.5	<0.001	11
ChorBF, P.U.	406.5 ± 19.7	339.4 ± 24.8	−16.2 ± 4.9	0.025	11
PP, mm Hg	51.7 ± 1.0	62.9 ± 1.6	21.7 ± 2.4	<0.001	11
ChorR, mm Hg/P.U.	0.13 ± 0.01	0.20 ± 0.02	51.6 ± 10.6	0.020	11
HR, bpm	194.1 ± 11.1	180.7 ± 16.5	−9.7 ± 5.9	NS	11

Parameter	Control	AVP (1.33 ng/kg/min)	Change (%)	P	n
MAP, mm Hg	64.0 ± 0.3	74.3 ± 1.8	16.0 ± 2.9	<0.001	11
IOP, mm Hg	12.3 ± 0.9	10.6 ± 0.8	−14.4 ± 2.1	<0.001	11
OVP, mm Hg	2.0 ± 0.2	0.9 ± 0.2	−53.8 ± 6.9	<0.001	11
ChorBF, P.U.	406.5 ± 19.7	287.8 ± 29.9	−28.7 ± 6.7	<0.001	11
PP, mm Hg	51.7 ± 1.0	63.7 ± 1.9	23.4 ± 3.7	<0.001	11
ChorR, mm Hg/P.U.	0.13 ± 0.01	0.25 ± 0.03	95.7 ± 24.1	<0.001	11
HR, bpm	194.1 ± 11.1	173.9 ± 16.3	−13.1 ± 5.9	0.002	11

portal vasculature maintain fluid balance by monitoring osmolality.²³ Arterial and atrial baroreceptors respond to alterations in blood volume and arterial pressure.²⁴ Although mechanisms regulating osmotic pressure are susceptible to small changes (2% increase in plasma osmolality evokes maximal antidiuresis), arterial pressure-induced AVP release is less sensitive (15%–20% decrease of arterial pressure caused maximal antidiuresis).²⁵ Malfunction of the AVP system is associated with a variety of water-retaining and cardiovascular diseases, and AVP is discussed in connection with subarachnoid hemorrhage and vasospasm.^{26–28} This is of particular interest to the eye because the vasospastic syndrome is considered to be a possible risk factor for the progression of normal tension glaucoma.^{29–32}

Systemic Effects of AVP

Intravenous infusion of AVP induced a dose-dependent increase in MAP (Fig. 3A) and a decrease in HR (Fig. 3B) caused by the constriction of vessels and the activation of the baroreflex. These findings were not surprising because similar systemic changes were previously reported in anesthetized hamsters and dogs.^{33–35} The effect of AVP on blood pressure is thought to be caused by the vasoconstriction of large, but not of smaller arterioles.³⁴ Given that the blood draws for AVP measurements would have caused a total change of roughly 12% in blood volume in the rabbit circulation, it seemed pertinent to replace the drawn volume immediately to avoid changes in blood pressure. On the other hand, this might have caused changes in the viscosity of blood and the hematocrit. Because both variables potentially have an impact on the number of Doppler shifts per time and on the other magnitude of the frequency shift, we measured the intensity response of four rabbits applying the same protocol (see Methods) but without

blood draws between measurements. The results were not different from the data presented in Table 1 and Figure 3, indicating that the blood draws had no significant effect on the measured variables (comparison not shown).

AVP and ChorBF Regulation

AVP acts via three types of G-protein-coupled vasopressin receptors: the V1 (V1a), V2, and V3 (V1b) receptors. It is supposed that the vasoactive property of AVP is based on the interaction with V1 and V2 receptors. Okamura et al.⁸ suggest that vasoconstriction is mediated by V1 receptors in vascular smooth muscle cells, whereas vasodilatation is associated with the NO release of endothelial cells after V2 receptor stimulation.³⁶ However, it has been observed that vasorelaxation at low AVP concentrations is also caused by V1 receptors assumed to be located in the vascular endothelium.⁸ It is hypothesized that vasoconstriction and vasodilatation are based on the complex interplay of signaling cascades in endothelial and vascular smooth muscle cells dependent on V1 and V2 receptors.³⁷

To determine the interaction between AVP and ChorBF regulation, MAP was changed by hydraulic occlusions of the descending aorta and the inferior caval vein, respectively. This caused changes in ocular PP over a wide range and stimulated regulatory mechanisms in the choroid and its supplying neuronal systems. The choroidal pressure-flow relationships showed regulatory plateaus at PP approximately >45 mm Hg. Below this pressure, the regulatory mechanisms are exhausted, maximum vasodilatation is reached, and blood flow becomes dependent on PP (Fig. 4, filled circles).

Intravenous application of AVP causes a dose-dependent downward shift of the choroidal pressure-flow relationship—

FIGURE 3. Effect of increasing plasma concentrations of AVP on measured parameters. (A) MAP, (B) HR, (C) IOP, (D) OVP, (E) ChorBF, (F) ChorR. All data are expressed as mean $\pm$ SEM ($n = 11$). The significance of change compared with control is indicated by * $P < 0.05$ and ** $P < 0.001$, respectively.

that is, at a certain PP ChorBF is reduced by vasoconstriction in the choroidal vascular bed. As opposed to high-dose AVP, by which vasoconstriction is obvious at all PPs, Figure 4 also shows that the vasoconstriction of low-dose AVP cannot be detected at baseline PP. The choroidal system has to be challenged by lowering PP until the vasoconstriction becomes obvious at PPs < 45 mm Hg (Fig. 4, open circles). Baseline changes did not predict this behavior, indicating that at a certain plasma concentration the effect of AVP on the choroidal circulation is highly dependent on PP across the vascular bed. It also means that the effects of drugs can be missed if the measurements are performed without manipulations of PP and at baseline only. This finding is of particular interest because low blood pressure has recently been linked to the risk for glaucoma and glaucoma progression.^{20,38} It might very well be the case that exogenous or endogenous vasoactive agents such as AVP might become effective only at low blood pressure, and without perturbation of PP their presence might not be considered important. In addition, it has been reported that increased AVP plasma levels after subarachnoid hemorrhage correlate with cerebral vasospasms in a rat model.^{27,39} The present study clearly demonstrates that AVP induces choroidal vasoconstriction in a dose-dependent manner (Fig. 3F). It is unknown whether vasoconstrictions caused by increased AVP plasma levels are of any importance in the pathogenesis of

ocular disease. However, given that the occurrence of vasospastic syndrome is discussed as a possible risk factor in the pathogenesis of glaucoma,^{30,31} it seems feasible to consider AVP as a possible link between the occurrence of a vasospastic syndrome and certain ocular pathologies such as the progression of glaucoma.

AVP and IOP

The effect of AVP on IOP is still matter of ongoing research, and the results reported in the literature are conflicting. Experimental approaches for investigating the effect of AVP on IOP include intraocular (anterior chamber or vitreous chamber),¹⁰ intracerebroventricular (third ventricle),^{10,11} topical,^{12,13} subconjunctival,¹² and intravenous^{10,12} application of AVP. Depending on the type of AVP application, different results were obtained. While IOP was elevated after intracerebroventricular injection,^{10,11} IOP was lowered after topical, intraocular, and intravenous administration.^{10,12,13} Although this study was performed in the acute rabbit preparation, the results confirm the dose-dependent reduction of IOP after intravenous AVP application (Fig. 3C). Gondim et al.¹⁰ hypothesized that the contrary effect of intravenous and intracerebroventricular application of AVP might be attributed to different regulatory mechanisms inside and outside the CNS. This is supported by the fact that

FIGURE 4. Choroidal pressure-flow relationships. Choroidal pressure-flow relationships are shown at control (black circles) and in response to low (0.08 ng/kg/min, open circles) and high (1.33 ng/kg/min, open squares) infusion rates of AVP. The control pressure-flow relationship shows a regulatory response to changes in PP. Although the pressure-flow relationship was not changed by the low infusion rate at baseline PP, it was significantly shifted downward at PP < 45 mm Hg (open circles). The high infusion rate causes a downward shift of the pressure-flow relationship at all PP (open squares) compared with control and with the low-infusion pressure-flow relationship. The data clearly demonstrate that drug effects on the choroidal circulation might remain unrecognized unless PP is changed. All data are shown as mean $\pm$ SEM. * $P < 0.05$.

intravenous administration of AVP has no impact on AVP levels in the cerebrospinal fluid.¹⁰ The current understanding of the receptor mechanisms by which AVP interacts with IOP homeostasis is not conclusive. Inhibition of the AVP-mediated effect on IOP by the selective V1-receptor antagonist, [β -mercapto- β , β -cyclopentamethylenepropionyl,¹ O-me-Tyr,² and Arg⁸]-vasopressin, suggests that the IOP-lowering effect is mediated by the V1 receptor.¹⁰ In contrast to Wallace et al.,⁴⁰ Gondim et al.¹⁰ observed no influence at intravenous injection of the selective V2 agonist, desmopressin, on IOP in rabbits. In the rabbit model of ocular hypertension, the selective nonpeptide V2 receptor antagonist SR121463, a compound that causes aquaresis, decreased IOP.^{41,42} Because of the ambivalent results, the underlying mechanisms remain to be discovered. However, identification of the vasopressin receptors involved in IOP and ocular blood flow regulation was beyond the scope of this study.

AVP and OVP

The role of OVP in the homeostasis of IOP and ocular hemodynamics is not yet fully understood. However, it has been shown that OVP, measured through the orbital venous sinus, is a dynamic parameter that correlates well with episcleral venous pressure and depends on the inflow of blood from the eye.¹⁴ In addition, the orbital venous sinus receives blood via low-resistance vessels from other regions in the head.⁴³ Consequently, the blood from the eye is only a small fraction of the total blood volume draining into the sinus. During acute manipulations of MAP, it has been shown that the MAP-OVP and the OVP-IOP relationships are linear—a decrease in MAP is accompanied by a decrease in OVP and IOP and vice versa.¹⁴ The present results show that OVP is altered not only by changes in MAP and PP, respectively, but also by intravenous application of AVP. On the one hand, the change in the percentage of baseline reaches up to more than 50% (Fig. 3D). On

the other hand, the changes in absolute values are rather small, and their physiological relevance seems questionable. In addition, comparisons between the literature and the present experiments have to be drawn with caution, because the time course of the manipulations (ranging from short term to long term) critically affects the relationship and the size of the effects measured. However, AVP application causes an increase in MAP and a decrease in OVP and IOP, indicating a significantly reduced blood flow and vasoconstriction in the ocular tissues. Because of the small contribution of the ocular circulation to OVP, the pronounced decrease in OVP suggests that vasoconstriction also occurs in other supplying areas of the orbital venous sinus, such as the brain.

Conclusions

In conclusion, AVP is a potent vasoactive substance involved in the homeostatic regulation of choroidal hemodynamics and ocular hydrodynamics. In the choroidal vascular bed, AVP causes dose-dependent constriction of vessels and, apart from modulating vascular tone, AVP also influences IOP in a dose-dependent manner. Understanding the mechanisms by which AVP interacts with the regulatory systems of ocular hemodynamics and hydrodynamics might give rise to new strategies for the development of drugs in the treatment of diseases with impaired ocular blood flow, IOP, or both. Although, to the best of our knowledge, the scientific literature provides no evidence for major differences between drug effects on ChorBF in the present rabbit model and in humans, the results should be cautiously compared with the situation in humans or other mammals. However, animal models provide a profound basis for understanding both direct and indirect mechanisms on vascular functions under physiological and pathophysiological conditions.

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