EXTENDED REPORT

Intravenous administration of clonidine reduces intraocular pressure and alters ocular blood flow

Günther Weigert, Hemma Resch, Alexandra Luksch, Herbert A Reitsamer, Gabriele Fuchsjäger-Mayrl, Leopold Schmetterer, Gerhard Garhofer

Br J Ophthalmol 2007;**91**:1354–1358. doi: 10.1136/bjo.2007.116574

See end of article for authors' affiliations

Correspondence to: Gerhard Garhofer, Department of Clinical Pharmacology, Medical University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria; gerhard.garhofer@meduniwien.ac.at

Accepted 3 May 2007
Published Online First
30 May 2007

Aim: To evaluate the effect of intravenously administered clonidine on ocular blood flow in healthy volunteers. **Methods:** A randomised, double-masked, placebo-controlled, two-way crossover study was performed in 12 healthy young volunteers. Clonidine (0.2 µg/kg/min) or placebo was administered intravenously over 10 minutes. The effects of clonidine were studied at baseline and up to 150 minutes after infusion. Ocular haemodynamics were measured using laser Doppler flowmetry, laser Doppler velocimetry and a retinal vessel analyser.

Results: Clonidine significantly decreased mean arterial pressure (MAP) and intraocular pressure (IOP). Calculated ocular perfusion pressure decreased significantly by $-8.7 \pm 8.7\%$ after infusion of clonidine ($p < 0.01$ vs placebo). Retinal arterial diameters increased by $+4.4 \pm 2.7\%$ ($p = 0.012$ vs placebo), whereas no significant change was observed in retinal veins. Red blood cell velocity decreased by $-16 \pm 14\%$ ($p < 0.01$ vs placebo) after infusion of clonidine. Hence, calculated retinal blood flow decreased by $-14 \pm 12\%$ ($p = 0.033$ vs placebo). Choroidal blood flow increased by $+18 \pm 19\%$ ($p < 0.01$ vs placebo) and optic nerve head blood flow increased by $+16 \pm 23\%$ ($p = 0.046$ vs placebo) 30 minutes after administration of clonidine but both returned to baseline thereafter.

Conclusion: The short-time increase in choroidal and optic nerve head blood flow indicates a transient vasodilatory effect of clonidine due to an unknown mechanism. The decrease in retinal blood flow indicates clonidine-induced vasoconstriction in the retinal microvasculature.

Alpha-2 receptor agonists effectively reduce intraocular pressure (IOP) after systemic as well as after topical administration making them an attractive option in glaucoma treatment.^{1–5} However, in view of the fact that besides increased IOP, reduced ocular blood flow appears to be related to the progression of glaucoma, the evaluation of potential vasoactive effects of anti-glaucoma drugs has gained much interest. With α₂ receptor agonists potent vasoconstrictor effects have been observed in several vascular beds including the eye.⁶

In the present study we have investigated the effect of the α₂ agonist clonidine on retinal, choroidal and optic nerve head blood flow. Clonidine, a derivative of imidazol, is used therapeutically to reduce systemic blood pressure based on a stimulation of adrenergic receptors on nerves and imidazol receptors in the brain.⁷ Additionally, it has been shown that clonidine decreases IOP regardless if administered systemically or topically.^{1–5} The early phase of the IOP-lowering effect has been mainly attributed to the vasoconstrictor potential of clonidine in the ciliary body.⁶ This is in good agreement with data of the α₂ receptor agonist brimonidine showing that the IOP decrease is initially due to a decrease in aqueous flow because of ciliary body vasoconstriction and after chronic treatment caused by an increase in uveoscleral outflow.^{8,9} Furthermore, there is evidence that topical administration of clonidine reduces ocular fundus pulsation amplitude, indicative for a reduction in choroidal blood flow.¹⁰ However, whether α₂ agonists may reduce retinal blood flow due to a potential vasoconstrictor effect in the posterior pole of the eye, or may even increase ocular blood flow due to a reduction of IOP and the concomitant increase in ocular perfusion pressure (OPP) remains unclear. A reduction in ocular blood flow may possibly limit the use of this class of drugs at least in some patients, because optic nerve head ischaemia appears to be a contributing factor in glaucoma pathophysiology.¹¹

In the current study we were especially interested in the haemodynamic effects of α₂ agonists in the posterior pole of the eye. Since topical administration of a drug always raises the question of drug concentration in the retina and choroid, we have selected a different approach. To assess the vasoactive properties of clonidine intravenous administration was chosen. This has the disadvantage that the interpretation of the data is complicated by changes in systemic blood pressure as caused by clonidine, but allows for the investigation of the drug effect of α₂ agonists under well-controlled conditions.

MATERIALS AND METHODS

Subjects

The study was performed in accordance with the guidelines of the Declaration of Helsinki and the Good Clinical Practice guidelines. The study protocol was approved by the ethics committee of the Medical University of Vienna. Twelve healthy non-smoking volunteers were included in the study. After signing a written informed consent, all participating subjects passed a screening examination including ophthalmic examination, medical history, physical examination, 12-lead ECG, complete blood count, coagulation parameters, clinical chemistry, blood serology, urine analysis and a urine drug-screening.

Study design

The study was performed in a randomised, double-masked, placebo-controlled, two-way crossover design. On two separate study days subjects received either 0.2 µg/kg/min clonidine (CATAPRESAN, Boehringer Ingelheim, Vienna, Austria) or placebo (physiological saline solution) intravenously for

Abbreviations: IOP, intraocular pressure; LDF, laser Doppler flowmetry; MAP, mean arterial pressure; OPP, ocular perfusion pressure; RBCs, red blood cells

10 minutes in a balanced randomised order using a volume-controlled pump. All subjects were studied under dilated pupil.

Experimental paradigm

After a 20-minute resting period in a sitting position, baseline measurements of blood pressure, pulse rate, ocular haemodynamics (Retinal vessel analyser, laser Doppler velocimetry, laser Doppler flowmetry in the macula and the optic nerve head) and IOP were performed. Thereafter, clonidine (0.2 µg/kg/min) or placebo was administered intravenously over 10 minutes. Haemodynamic measurements were repeated 30, 70, 110 and 150 minutes after starting the infusion. Blood pressure was measured in 5 minute intervals throughout the whole study period and pulse rate and ECG were monitored continuously. The washout period between the two study days was at least 5 days.

Methods

Systolic, diastolic and mean arterial (MAP) blood pressures were measured on the upper arm by an automated oscillometric device. Pulse rate was automatically recorded from a finger pulse-oxymetric device. An ECG was monitored continuously using a standard four-lead device (HP-CMS patient monitor, Hewlett Packard, Palo Alto, USA).

Measurement of IOP

The IOP was measured with a Goldmann applanation tonometer (Haag Streit Applanation Tonometer AT 900, Haag Streit, Koenitz, Switzerland). Oxybuprocaine hydrochloride was used to anaesthetise the cornea.

Laser Doppler flowmetry

Choroidal and optic nerve head blood flow were assessed with laser Doppler flowmetry (LDF) according to Riva *et al.* (Oculix 4000, Oculix Sarl, Arbaz, Switzerland).^{12, 13} The principles of LDF have been described in detail by Bonner and Nossal.¹⁴ Briefly, the vascularised tissue is illuminated by coherent laser light. Scattering on moving red blood cells (RBCs) leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency but lead to randomisation of light directions impinging on RBCs. This light diffusing in vascularised tissue leads to a broadening of the spectrum of scattered light (Doppler shift power spectrum). From this the mean RBC velocity, the blood volume and the blood flow can be calculated in relative units. In the present study the laser beam was directed to the fovea to assess blood flow in the submacular choroid.¹² Blood flow in the optic nerve head was measured at the temporal neuroretinal rim.¹³ Care was taken that the measurement location did not include any visible larger vessels.

Laser Doppler velocimetry

In the present study, a fundus camera-based system with a single mode laser diode at a centre wavelength of 670 nm was used (Oculix Sarl, Arbaz, Switzerland). The principle of blood flow velocity measurement by laser Doppler velocimetry is based on the optical Doppler effect. Laser light, which is scattered by moving particles (eg, erythrocytes), is shifted in frequency. This frequency shift is proportional to the blood flow velocity in the retinal vessel.^{15, 16} The maximum Doppler shift corresponds to the centreline erythrocyte frequency. Measurements were done in main inferior temporal retinal veins.

Retinal vessel analyser

The retinal vessel analyser (Imedos, Jena, Germany) is a commercially available system, which comprises a fundus

camera, a video camera, a high-resolution video recorder, a real-time monitor and a personal computer with a vessel analysing software for the accurate determination of retinal arterial and venous diameters with a time resolution of 25 readings/second.¹⁷ The fundus is illuminated with light in the range of wavelengths between 567 and 587 nm. The system provides excellent reproducibility and sensitivity.¹⁸ Major temporal arteries and veins were studied in the current study. RBC velocity was measured at the same locations as retinal vessel diameters by using bidirectional laser Doppler velocimetry.

Calculation of retinal blood flow

Retinal blood flow was calculated from maximum erythrocyte velocity (Vmax) using laser Doppler velocimetry and retinal vessel diameters using the retinal vessel analyser. Mean blood velocity in retinal veins was calculated as (Vmax/2). Blood flow through a specific retinal vein was then calculated as $Q = (V_{\text{max}}/2) \cdot (\pi \cdot d^2/4)$, whereas d is the diameter of the vein.

Data analysis

Statistical analysis was carried out using the Statistica software package (StatSoft, Melbourne, Australia). Changes in haemodynamic parameters were calculated as % change over baseline values (if not otherwise stated, data 150 minutes after the start of infusion are presented). A two-way repeated measures ANOVA model was used for statistical analysis. Statistical differences between clonidine and placebo were calculated as the interaction between time and treatment. Post-hoc analysis was carried out by planned comparisons. $p < 0.05$ was considered as the level of significance.

Results

Intravenous administration of clonidine in the selected dose was well tolerated by all subjects. None of the subjects experienced headache or discomfort. No adverse event occurred during the study.

Systemic haemodynamics and IOP

Baseline blood pressure and pulse rate was comparable on both study days (table 1). As shown in fig 1, intravenous administration of clonidine significantly decreased MAP from 76 ± 7 mm Hg to 64 ± 5 mm Hg after 150 minutes, whereas MAP remained unchanged in the placebo group (ANOVA, $p < 0.01$ vs placebo). In the clonidine group pulse rate decreased during the administration of clonidine (ANOVA, $p < 0.01$ baseline vs time), but no significant difference was observed between the two groups (ANOVA, $p = 0.27$ placebo vs treatment). As expected, clonidine decreased IOP from 12 ± 2 mm Hg to 8 ± 3 mm Hg (ANOVA, $p < 0.01$). This effect was still significant 150 minutes after the start of drug administration (fig 1), whereas placebo did not affect IOP. Calculated ocular perfusion pressure decreased significantly by $-8.7 \pm 8.7\%$ after infusion of clonidine (fig 1; ANOVA, $p < 0.01$ vs placebo).

Retinal blood flow

Baseline parameters are presented in table 1 and were not significantly different between study days. Retinal arterial diameters increased by $+4.4 \pm 2.7\%$ after administration of clonidine (fig 1; ANOVA, $p = 0.012$ vs placebo). By contrast, administration of clonidine did not affect retinal venous diameters ($+1.1 \pm 2.9\%$; fig 1; ANOVA, $p < 0.9$ vs placebo). Red blood cell velocity as assessed with bi-directional laser Doppler velocimetry decreased by $-16 \pm 14\%$ (fig 1; ANOVA, $p < 0.01$ vs placebo) after infusion of clonidine. Thus, calculated retinal blood flow decreased by $-14 \pm 12\%$ (fig 1; ANOVA, $p = 0.033$ vs placebo).

Figure 1 Intraocular pressure, mean arterial pressure, retinal arterial diameter, ocular perfusion pressure, optic nerve head (ONH) blood flow, choroidal blood flow, red blood cell velocity and calculated retinal blood flow after infusion of clonidine (solid triangles) and placebo (open circles). Data are presented as means $\pm$ SD. Asterisks show significant changes after infusion of clonidine.

Choroidal blood flow

Choroidal blood flow at baseline was comparable on the two study days. As shown in fig 1, choroidal blood flow increased by $+18 \pm 19\%$ at 30 minutes after infusion of clonidine (fig 1; ANOVA, $p < 0.01$ vs placebo). Seventy minutes after drug

administration, however, and at all subsequent time points no significant difference between placebo and clonidine was observed. Placebo did not influence choroidal blood flow.

Optic nerve head blood flow

Baseline optic nerve head blood flow did not differ between the two study days. Optic nerve head blood flow also increased after infusion of clonidine ($+16 \pm 23\%$; fig 1; ANOVA, $p = 0.046$ vs placebo) but again, this effect was only significant 30 minutes after drug administration. No significant difference between placebo and clonidine day was observed 70, 110 and 150 minutes after start of the infusion.

Discussion

Whereas the systemic haemodynamic effects of clonidine are well described, there is a longstanding discussion whether administration of α_2 agonists may lead to a decrease in ocular perfusion. Almost 30 years ago, evidence from rabbit experiments indicated that intravenous administration of clonidine leads to a heterogeneous effect on ocular blood flow with a decrease in blood flow in the choroid, the ciliary body and the

Table 1 Haemodynamic parameters at baseline

	Placebo	Clonidine
Systolic blood pressure (mm Hg)	115 ± 8	114 ± 10
Diastolic blood pressure (mm Hg)	61 ± 6	56 ± 7
Mean arterial pressure (mm Hg)	79 ± 6	76 ± 7
Pulse rate (bpm)	65 ± 8	63 ± 11
Intraocular pressure (mm Hg)	12 ± 3	12 ± 3
Retinal arterial diameter (μm)	125.1 ± 24.8	128.3 ± 21.5
Retinal venous diameter (μm)	150.8 ± 16.5	155.3 ± 14.6
Red blood cell velocity (cm/s)	2.1 ± 0.2	2.1 ± 0.2
Optic nerve head blood flow (AU)	6.3 ± 1.0	5.9 ± 1.1
Choroidal blood flow (AU)	8.0 ± 1.1	7.3 ± 1.4
Retinal blood flow ($\mu\text{l}/\text{min}$)	18.93 ± 5.28	19.85 ± 3.64
Ocular perfusion pressure (mm Hg)	40.8 ± 4.1	38.2 ± 3.4

Data are given in absolute values and are presented as means $\pm$ SD.

iris, and the opposite reaction in the retina and the optic nerve.²¹

Additional animal experiments showed that systemic administration of clonidine constricts episcleral and conjunctival vessels, but does not affect the fundus vessels of rabbits.²² Studies in isolated vessels, however, revealed no significant change in diameter of canine internal, external ophthalmic and ciliary arteries in response to clonidine.²³

However, the interpretation of the effects of systemically administered clonidine is complicated by the fact that clonidine induces a combination of central and peripheral effects. Particularly, clonidine acts on central α_2 adrenoceptors leading to the inhibition of sympathetic vasoconstrictor centres thereby decreasing heart rate and vascular tone. This central effect, most likely mediated by α_{2a} receptors, is superposed by the local drug effects of clonidine in the periphery. Clonidine stimulates peripheral postsynaptic α_1 and α_2 adrenoceptors, leading to pronounced vasoconstriction, increased venous return and increased blood pressure.²⁴ Thus, the net effect observed after systemically administered clonidine is caused by a complex combination of centrally mediated sympatholytic together with vasoconstrictive effects caused by peripheral α receptors.

Despite these considerations, we have chosen intravenous administration of clonidine to investigate whether vasoconstrictor effects of clonidine, which might considerably decrease ocular blood flow, occur in the retina, because topical administration of a drug always raises the question about the availability of the substance at the site of action.

As expected, our data indicate a pronounced drop in IOP and MAP after administration of clonidine. Since the decrease in MAP exceeds the decrease in IOP, a drop in ocular perfusion pressure was observed. In retinal arteries a slight increase in diameters was observed after drug administration, whereas no change in retinal venous diameters was evident. This retinal arterial vasodilatation could be in part a result of an autoregulatory response to the decrease in perfusion pressure. Alternatively, one could hypothesise that the increase in retinal arterial diameters could be at least partially caused by a lowered systemic catecholamine level, as it is usually induced by the central effects of clonidine.²⁵ Measurement of systemic catecholamine levels, however, would be necessary to prove this hypothesis. Moreover, a reduction in pulse rate was observed after administration of clonidine, as usually seen with this drug. However, statistical difference in pulse rate between clonidine and the placebo group failed to reach significant levels, most probably, because of a slight reduction of pulse rate in the placebo group.

In addition, a decrease in retinal blood flow was observed after administration of clonidine. This decrease in retinal blood flow can be attributed to the decrease of RBC velocity as measured in retinal veins. We can not entirely exclude that the decrease in OPP is in part responsible for reduced retinal blood flow, but it appears unlikely, because the retina is autoregulated over a wide range of OPPs and there is little evidence to assume that α receptors are involved in this regulatory process.^{26, 27} Hence, the decreased retinal blood velocity more likely reflects a clonidine-induced vasoconstriction in the retinal microvasculature. To finally prove this hypothesis a quantification of changes of retinal microvessels would be required, which unfortunately, is difficult because of the limited resolution of techniques currently available.

The data of choroidal and optic nerve head blood flow in the present study are somewhat unexpected, because administration of clonidine leads to a transient increase of perfusion in tissues, the choroid and the optic nerve head. This increase was only observed 30 minutes after administration of clonidine and

was obvious in almost all volunteers in both vascular beds. The reason for this difference in the pharmacodynamic behaviour in the different vascular beds remains speculative. At least two mechanisms could be responsible for the transient blood flow increase. First, one cannot exclude that clonidine acts directly via α receptors in choroidal and optic nerve head vessels. Pharmacological²⁸ and histochemical studies^{29, 30} indicate that α adrenergic receptors are present on choroidal vessels. However, a direct vasodilator effect of clonidine is unlikely, because several studies demonstrate that direct electrical stimulation of the ocular sympathetic nerves or infusion of catecholamines lead to a local vasoconstriction and consequently a decrease of choroidal blood flow.^{29–31}

As stated above, both local and central effects of clonidine have to be taken into consideration with regard to the ocular haemodynamic effects of the drug. Clonidine reduces sympathetic tone via central stimulation of α receptors.³² Activation of these central receptors reduces peripheral resistance and leads to a reduction of systemic blood pressure. Thus, alternatively, one could hypothesise that the decrease in sympathetic activity may lead to a choroidal vasodilation and, in turn, to an increase of choroidal blood flow. This seems reasonable, because in contrast to the retinal circulation, the choroid is strongly innervated by the autonomic nervous system. Furthermore, this idea is also supported by previous evidence indicating peripheral vasoconstriction of clonidine after eliminating concomitant, centrally mediated sympatholytic effects by anaesthetising the brachial plexus in a forearm blood flow model.³³ Following this line of thought, this may indicate that in the choroid, as evidenced for other vascular beds, the peripheral vasoconstrictive effects of α_2 agonists are masked by the simultaneous central sympatholytic effects. Further studies are, however, required to clarify this issue.

Our data clearly show a decrease in retinal blood flow after systemic administration of clonidine, indicating an increase in vascular resistance after administration of adrenergic agonists. Whether this also holds true for the topical long-term administration of clonidine or other α_2 adrenergic agonists has yet to be clarified.

Authors' affiliations

Günther Weigert, Hemma Resch, Alexandra Luksch, Gabriele Fuchsjäger-Mayrl, Leopold Schmetterer, Gerhard Garhofer, Department of Clinical Pharmacology, Medical University of Vienna, Austria
Günther Weigert, Alexandra Luksch, Gabriele Fuchsjäger-Mayrl, Gerhard Garhofer, Department of Ophthalmology, Medical University of Vienna, Austria
Herbert A Reitsamer, Department of Ophthalmology and Optometry, Paracelsus University Salzburg, Austria
Leopold Schmetterer, Center of Biomedical Engineering and Physics, Medical University of Vienna, Austria

Funding: Supported by Grant 11214 from the Jubiläumsfonds der Österreichischen Nationalbank.

Competing interests: None declared.

REFERENCES

- 1 **Abrams DA**, Robin AL, Crandall AS, *et al*. A limited comparison of apraclonidine's dose response in subjects with normal or increased intraocular pressure. *Am J Ophthalmol* 1989;**108**:230–7.
- 2 **Abrams DA**, Robin AL, Pollack IP, *et al*. The safety and efficacy of topical 1% ALO 2145 (p-aminoclonidine hydrochloride) in normal volunteers. *Arch Ophthalmol* 1987;**105**:1205–7.
- 3 **Chiou GC**. Effects of alpha 1 and alpha 2 activation of adrenergic receptors on aqueous humor dynamics. *Life Sci* 1983;**32**:1699–704.
- 4 **Nagashubramanian S**, Hitchings RA, Demailly P, *et al*. Comparison of apraclonidine and timolol in chronic open-angle glaucoma. A three-month study. *Ophthalmology* 1993;**100**:1318–23.
- 5 **Wilensky JT**. The role of brimonidine in the treatment of open-angle glaucoma. *Surv Ophthalmol* 1996;**41**:S3–7.

- 6 **Wikberg-Matsson A**, Simonsen U. Potent alpha(2A)-adrenoceptor-mediated vasoconstriction by brimonidine in porcine ciliary arteries. *Invest Ophthalmol Vis Sci* 2001;**42**:2049–55.
- 7 **Meeley MP**, Ernster P, McCauley PM, et al. Clonidine-specific antibodies as models for imidazole and alpha 2-adrenergic receptor binding sites: implications for the structure of clonidine-displacing substance. *J Hypertens* 1988;**6**:S490–3.
- 8 **Reitsamer HA**, Posey M, Kiel JW. Effects of topical alpha2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. *Exp Eye Res* 2005;**82**:405–15.
- 9 **Toris CB**, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. *Am J Ophthalmol* 1999;**128**:8–14.
- 10 **Schmetterer L**, Strenn K, Findl O, et al. Effects of antiglaucoma drugs on ocular hemodynamics in healthy volunteers. *Clin Pharmacol Ther* 1997;**61**:583–95.
- 11 **Flammer J**, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002;**21**:359–93.
- 12 **Riva CE**, Cranston SD, Grunwald JE, et al. Choroidal blood flow in the foveal region of the human ocular fundus. *Invest Ophthalmol Vis Sci* 1994;**35**:4273–81.
- 13 **Riva CE**, Harino S, Petrig BL, et al. Laser Doppler flowmetry in the optic nerve. *Exp Eye Res* 1992;**55**:499–506.
- 14 **Bonner R**, Nossal R. Principles of laser-Doppler flowmetry in laser-Doppler blood flowmetry. In: Shepard AP, Öberg AP, eds. *Vol 107 of Developments in cardiovascular medicine*. Boston: Kluwer Academic Publishers, 1990:17–45.
- 15 **Riva CE**, Grunwald JE, Sinclair SH. Fundus camera based retinal LDV. *Appl Opt* 1981;**20**:117–20.
- 16 **Riva CE**, Grunwald JE, Sinclair SH, et al. Blood velocity and volumetric flow rate in human retinal vessels. *Invest Ophthalmol Vis Sci* 1985;**26**:1124–32.
- 17 **Blum M**, Bachmann K, Wintzer D, et al. Noninvasive measurement of the Bayliss effect in retinal autoregulation. *Graefes Arch Clin Exp Ophthalmol* 1999;**237**:296–300.
- 18 **Polak K**, Dörner G, Kiss B, et al. Evaluation of the Zeiss retinal vessel analyser. *Br J Ophthalmol* 2000;**84**:1285–90.
- 19 **MacMillan LB**, Hein L, Smith MS, et al. Central hypotensive effects of the alpha2a-adrenergic receptor subtype. *Science* 1996;**273**:801–3.
- 20 **Link RE**, Desai K, Hein L, et al. Cardiovascular regulation in mice lacking alpha2-adrenergic receptor subtypes b and c. *Science* 1996;**273**:803–5.
- 21 **Kaskel D**, Mergelsberg M, Rudof H, et al. [Blood flow through different tissues under clonidine in rabbits (author's translation)]. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1976;**201**:149–58.
- 22 **Baurmann H**, Jankolovitz M, Wirmmer M, et al. [Simultaneous study of ocular vascular reactions of the anterior and posterior segments following clonidine and propranolol in normotensive and hypertensive experimental animals]. *Klin Monatsbl Augenheilkd* 1986;**189**:467–76.
- 23 **Ohkubo H**, Chiba S. Pharmacological analysis of vasoconstriction of isolated canine ophthalmic and ciliary arteries to alpha-adrenoceptor agonists. *Exp Eye Res* 1987;**45**:263–70.
- 24 **MacMillan LB**, Hein L, Smith MS, et al. Central hypotensive effects of the alpha2a-adrenergic receptor subtype. *Science* 1996;**273**:801–3.
- 25 **Bravo EL**, Tarazi RC, Fouad FM, et al. Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;**305**:623–6.
- 26 **Dumskyj MJ**, Eriksen JE, Dore CJ, et al. Autoregulation in the human retinal circulation: assessment using isometric exercise, laser Doppler velocimetry, and computer-assisted image analysis. *Microvasc Res* 1996;**51**:378–92.
- 27 **Grunwald JE**, Sinclair SH, Riva CE. Autoregulation of the retinal circulation in response to decrease of intraocular pressure below normal. *Invest Ophthalmol Vis Sci* 1982;**23**:124–7.
- 28 **Kiel JW**, Lovell MO. Adrenergic modulation of choroidal blood flow in the rabbit. *Invest Ophthalmol Vis Sci* 1996;**37**:673–9.
- 29 **Koss MC**, Gherezghier T. Adrenoceptor subtypes involved in neurally evoked sympathetic vasoconstriction in the anterior choroid of cats. *Exp Eye Res* 1993;**57**:441–7.
- 30 **Koss MC**. Adrenoceptor mechanisms in epinephrine-induced anterior choroidal vasoconstriction in cats. *Exp Eye Res* 1994;**59**:715–22.
- 31 **Alm A**, Stjernschantz J, Bill A. Effects of oculomotor nerve stimulation on ocular blood flow in rabbits after sympathetic denervation. *Exp Eye Res* 1976;**23**:609–13.
- 32 **Szabo B**, Fritz T, Wedzony K. Effects of imidazoline antihypertensive drugs on sympathetic tone and noradrenaline release in the prefrontal cortex. *Br J Pharmacol* 2001;**134**:295–304.
- 33 **Talke PO**, Lobo EP, Brown R, et al. Clonidine-induced vasoconstriction in awake volunteers. *Anesth Analg* 2001;**93**:271–6.

Keep up to date: sign up for our alerting services

Find out automatically when an article is published on a specific topic or by a particular author. We can also alert you when an article is cited or if an eLetter or correction is published. You can also choose to be alerted when a new issue is published online [and when we post articles Online First]. Check out the New Content Alerts and Citation tracker from the Online tools section on the home page.