Angiotensin-II Contracts Isolated Human Posterior Ciliary Arteries

Niels C. Berg Nyborg and Per J. Nielsen

The effect of angiotensin-II (A-II) was studied on ring segments of the terminal extraocular branches of the posterior ciliary artery isolated from human enucleated eyes. It induced a potent concentration-dependent contraction on top of the spontaneous myogenic tone of all arteries studied from five patients with the concentration required to give half-maximal response equal to 51 nM. The spontaneous tone and maximal increase in vessel wall tension induced by A-II was equal to 51% of E_{max}. The relative response and sensitivity to A-II was unchanged in three endothelial denuded vessels, but the spontaneous tone increased. The arteries became completely insensitive to A-II after one exposure. These results show an immediate direct contractile effect of A-II on human posterior ciliary arteries, but the development of pronounced tachyphylaxis indicates that A-II is probably not an important factor in reducing blood flow to the optic nerve head. Invest Ophthalmol Vis Sci 31:2471-2473, 1990

Ischemic visual field defects may be due to a disturbed circulation in the prelaminar region of the optic disc. Angiotensin-II (A-II) binding sites and angiotensin-converting enzyme (ACE) activity have recently been detected in human, feline, and bovine retinal vascular tissue. This may thus suggest that either locally formed or blood-borne A-II may interfere with ocular blood flow. We previously showed that bovine retinal arteries are insensitive to A-II, although A-II contracts the posterior ciliary arteries. In these experiments we studied the reactivity of arterial ring segments of the posterior ciliary artery from humans to A-II.

Materials and Methods. Enucleated eyes from patients (aged, 66 ± 5 yr; n = 5), admitted to eye departments at the regional hospitals throughout the peninsula of Jutland, were placed in ice-cold physiologic saline solution (PSS) with the following composition: NaCl 117 mM, NaHCO3 25 mM, KCl 4.7 mM, CaCl2 1.5 mM, MgSO4 1.18 mM, KH2PO4 1.17 mM, ethylenediaminetetraacetic acid 0.026 mM, and glucose 11 mM. Transport time did not exceed more than 3 hr. None of the patients had received drugs inhibiting the A-II receptor or ACE system.

One or two segments of the terminal extraocular branches of either the medial or lateral posterior ciliary artery were isolated from human enucleated eyes. The vessels were transferred to an isometric myograph

Emax was measured as the difference in wall tension of the vessels, when they were fully contracted with acetylcholine (K-PSS to which 10^{-5} M 5-hydroxy-
tryptamine and prostaglandin F2α was added) and fully relaxed in Ca2+-free PSS (similar to PSS except that CaCl2 was replaced with 5 mM EGTA).

All drugs were prepared in stock solutions and stored in a freezer at −20°C until use. The drugs were added to the organ chamber on the myograph in volumes not exceeding 0.1% to reach final required concentration. The concentration of A-II required to give half-maximal response \( [EC_{50}(M)] \) was calculated by nonlinear curve fitting of concentration-response data to the equation \( \frac{R}{R_{\text{max}}} = \frac{A(M)^p}{(A(M)^p + EC_{50}(M)^p)} \), with concentration \( A(M) \) on a log scale. \( R/R_{\text{max}} \) is the relative active response to drug, and \( p \) is a curve-fitting parameter or “Hill coefficient.”

Responses of the vessels are either given as active wall tension, \( N/m \), calculated as increase in vessel wall force above resting level divided by twice the vessel segment length or in relative units. Student \( t \)-tests for unpaired data were used, and a probability, \( P \), less than 0.05 was considered significant.

**Results.** All endothelium intact posterior ciliary arteries (effective lumen diameter, 245 ± 18 μm; \( n = 6 \)) developed a spontaneous myogenic tone, 0.20 ± 0.11 N/m (\( n = 6 \)). Papaverine \( 10^{-4} \text{M} \) induced a prompt and maximal relaxation (Fig. 1A).

A-II induced a concentration-dependent contraction of all endothelium-intact posterior ciliary arteries (Fig. 1B). The average vessel sensitivity (−log\( EC_{50}(M) \)) was 8.48 ± 0.11 (\( n = 6 \)) (\( EC_{50}(M) \) = 51 nM). The maximal A-II-induced contraction was 0.89 ± 0.16 N/m (\( n = 6 \)). The spontaneous tone plus the tone induced by A-II corresponded to 51 ± 9% of E\(_{\text{max}}\) (2.29 ± 0.40 N/m, \( n = 6 \)). The sensitivity to A-II of the arteries was not correlated with age or vessel lumen diameter. The maximal relaxation induced by acetylcholine, 85 ± 6% (\( n = 6 \)), was not different from the relaxation induced by sodium nitroprusside (\( 10^{-4} \text{M} \), 93 ± 7% (\( n = 6 \)), and A-II had no effect on vessels exposed a second time, indicating complete desensitization of the posterior ciliary arteries to A-II.

The sensitivity (−log\( EC_{50}(M) \))−value = 8.29 ± 0.26; \( n = 3 \) was not changed in endothelium-denuded vessels. The maximal tension induced by A-II (0.41 ± 0.26 N/m; \( n = 3 \)) in vessels without endothelium was not statistically different from that of intact arteries. The spontaneous tone plus that induced by A-II, 88 ± 4% (\( n = 3 \)) of E\(_{\text{max}}\), was significantly greater \(( P < 0.05)\) than in normal arteries. Acetylcholine did not relax any of the endothelium-denuded vessels.

**Discussion.** These experiments showed that human posterior ciliary arteries are sensitive to A-II and that A-II seemed to induce a greater contraction in human posterior ciliary arteries than in bovine posterior ciliary arteries.\(^5\) The contraction could only be elicited once; thereafter the vessels became completely insensitive to A-II. That the contraction could only be elicited once indicates that A-II may have little and no permanent effect on the human optic disc circulation. However, we cannot exclude the possibility that a secondary arterial constriction might develop, which may compromise the blood flow, due to an A-II-dependent potentiation of the sympathetic neurotransmission in the vessel wall.\(^9\) Furthermore, our data can neither be used to prove or disprove an A-II-mediated contraction of the arteries in the prelaminar region of the optic nerve head.\(^9\)

The mechanical data on the arteries indicate that the arteries are not appreciably damaged during transportation, because their ability to develop spontaneous myogenic tone in vitro was preserved, and the maximal force generation was high. The vascular endothelium was also still able to induce relaxation after acetylcholine stimulation to the same degree as sodium nitroprusside, indicating very little or no damage to the endothelium.

It is now known that the vascular smooth muscle tone in addition to being regulated by the vascular neuronal activity, also is regulated by factors released from the endothelium, eg, prostacyclin and endothelium-derived relaxing factor (EDRF or NO).\(^10\)\(^11\) Our experiments did not indicate that the presence of endothelium played any significant role in the direct contractile effect of A-II.

This does, however, not exclude a role of the endothelium itself in the process of mediating inappropriate arterial contraction. It has been demonstrated in a number of vessel preparations that both prostacyclin\(^9\) and EDRF may be released spontaneously\(^12\) and exert a continuously relaxing stimulus on the underlying vascular smooth muscle. Damage of the endothelium would then, when the vascular smooth muscle has the ability to contract spontaneously as shown for human posterior ciliary arteries, lead to contraction of the artery segment. Our experiments indicate that damage to the ciliary artery endothelium augments the total force generation of these vessels in

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**Fig. 1.** Tracings showing the relaxing effect of \( 10^{-4} \text{M} \) papaverine (A) and the contractile effect of A-II, \( 10^{-10} \text{M} \) to \( 10^{-6} \text{M} \) (B), on a human posterior ciliary artery. Concentration of A-II is given as log (concentration, M). Vertical scale shows force in mN (milliNewton) and horizontal bar shows time.
Decreased Dopamine in the Retinas of Patients With Parkinson’s Disease

Carmen Harnois,* and Thérèse Di Paolo†

Dopamine and its metabolites dihydroxyphenylacetic acid and homovanillic acid were measured in the retinas of eight patients with Parkinson disease who died. They were divided into two groups according to their last dose of levodopa therapy. One group of three patients had not received levodopa therapy for at least 5 days before death, and the other group of five patients had received therapy 2–15 hours before death. Each patient was matched with controls for delay between death and freezing. In the three patients without levodopa therapy, the retinal dopamine content was lower than normal. In the five patients who received levodopa therapy before death, the retinal dopamine content was similar to that in the controls. This study is the first direct evidence to the authors’ knowledge that retinal dopamine concentration is decreased in Parkinson’s disease, as it is in the nigrostriatal pathway. Invest Ophthalmol Vis Sci 31:2473–2475, 1990.

Dopamine (DA) is a neurotransmitter in the retina. There are two pathologic disorders of the dopaminergic system: Parkinson’s disease and diabetes. The former is characterized by a loss of dopaminergic neurons in the nigrostriatal pathway and a marked impairment in the motor system. In addition, there are clinical reports of alterations in the visual system of patients with parkinsonism. Increased latency of the visual-evoked potentials and contrast-sensitivity loss have been observed. Thus DA depletion in the central nervous system may cause the visual abnormalities. However, more recent studies describe abnormal electroretinograms in these patients, either after flash stimulation or pattern stimulation. These results suggest that the visual system abnormalities may be related to retinal DA depletion. Dopaminergic neurons have been identified in the retinas of different animal species, including humans. A recent study identified retinal dopaminergic neurons in patients with Parkinsonism by their tyrosine hydroxylase immunoreactivity; reduced DA

References


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From the Department of Pharmacology, Aarhus University, Aarhus C, and the Eye Department, Hjørring Hospital, Hjørring, Denmark.

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Reprint requests: Dr. Niels C. Berg Nyborg, Department of Pharmacology, Aarhus University, DK-8000 Aarhus C, Denmark.