

Evidence for a new role of natriuretic peptides: control of intraocular pressure

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Abstract

To study the possible physiological role of atrial natriuretic peptide (ANP) in the regulation of intraocular pressure (IOP) the effects of an increase of endogenous ANP within the physiological range induced by the neutral endopeptidase 24.11 (NEP) inhibitor candoxatril were examined. In a single masked placebo controlled trial, seven patients were studied with normal IOP (six male, one female; average age 50 (range 37-62 years). Intraocular pressure in each eye was measured after 2 weeks of placebo, after 4 weeks of candoxatril 200 mg twice daily, and during the first 3 days of placebo washout. With 4 weeks of candoxatril, endogenous plasma ANP levels increased from 4.2 (SEM 1.5) to 6.0 (1.5) pmol/l ($p < 0.04$) and there was a significant decrease in mean arterial pressure from 119 (4) to 110 (3) mm Hg ($p < 0.02$; 12 hours after treatment). There was a significant reduction in IOP after 4 weeks' treatment with candoxatril (right eye 2.1 (0.8) mm Hg, $p < 0.05$ paired *t* test, left eye 2.8 (0.8) mm Hg, $p < 0.02$). The mean fall in IOP was 11% (4%) in the right eye and 16% (3%) in the left eye and the fall in IOP was greater the higher the initial IOP. The reduction in IOP with chronic NEP inhibition was positively correlated with the increase in ANP levels but not with changes in blood pressure. These findings suggest that ANP may play a physiological role in the regulation of IOP. As the fall in IOP was greater in subjects with higher initial IOP, NEP inhibitors may be of therapeutic value in the management of glaucoma. (*Br J Ophthalmol* 1994; 78: 446-448)

A role for atrial natriuretic peptide (ANP) in the regulation of intravascular fluid volume and blood pressure is now well established.^{1,2} There is also preliminary evidence for pharmacological effects of ANP on the regulation of aqueous humour production and of intraocular pressure (IOP). Atrial natriuretic peptide has been identified in the anterior uvea in the rat,³ and specific receptors for ANP have been demonstrated in the pigmented epithelium of the ciliary processes in the rabbit.⁴ Intravenous or intravitreal injection of pharmacological doses of ANP cause a reduction in aqueous humour production and lower IOP in the rabbit.⁵⁻⁹ In primates, administration of ANP intravenously, or by injection into the anterior chamber of the eye, increases uveoscleral outflow.¹⁰ Furthermore, acute intravenous injection of high dose ANP in patients with pathologically raised IOP reduced the intraocular pressure by around 15%.¹¹

However, it is unclear whether ANP plays a physiological role in the regulation of IOP. Neutral endopeptidase (NEP) 24.11 inhibition is

an important mechanism for the normal catabolism of ANP. We therefore examined the possible physiological effects of ANP in the eye by studying IOP during acute and chronic elevation of endogenous ANP within the normal range by the oral prodrug candoxatril which is metabolised to the NEP 24.11 inhibitor UK 73 967.¹²

Materials and methods

We studied seven patients (six male, one female; average age 50 (range 37-62) years) with normal intraocular pressure (right eye 18 (SEM 1) mm Hg, range 11-22 mm Hg; left eye 17 (2) mm Hg, range 10-22 mm Hg) and average supine blood pressure 162/97 (10/1) mm Hg, who had been referred to the blood pressure unit of St George's Hospital by their general practitioners. The study was approved by the local hospital ethics committee and informed consent was obtained from each subject.

In this single masked study, there was a 2 week long placebo controlled run in period, followed by 4 weeks of active treatment with candoxatril (Pfizer Central Research, Sandwich, UK) 200 mg twice daily and a 1 week long placebo controlled washout period. In view of the important effects of dietary sodium intake on plasma ANP levels and on the response to NEP inhibition,¹² subjects were advised how to maintain a constant dietary sodium intake of around 150 mmol/day during the study.

For IOP measurements, both eyes were anaesthetised locally with one drop of 0.4% oxybuprocaine (Benoxinate; Smith & Nephew Pharmaceuticals, Romford, Essex) and readings were taken with the hand held Tonopen (Biorad, Glendale, CA, USA) with the patient in a sitting position.¹³ The IOP in each eye was taken as the mean of five recordings for each measurement time. Baseline IOP was taken as the average of measurements at 10 am on the morning before the last dose of placebo, at the end of the 2 week run in period, and at 10 am on the following morning before the first dose of active treatment with candoxatril. The acute effects of NEP inhibition on IOP were assessed by comparing the IOP during the 6 hours after placebo at the end of the 2 week run in period with IOP during the 6 hours after the first dose of active treatment with candoxatril on the following morning. To assess the IOP response to chronic NEP inhibition, baseline 10 am IOP was compared with 10 am IOP 12 hours after the last dose of candoxatril after 4 weeks of active treatment. IOP was also measured daily at 10 am for the initial 3 days of the placebo controlled washout period.

On each visit blood pressure was measured by a semiautomatic ultrasound sphygmomanometer (Arteriosonde, Roche, Cranbury, NJ,

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Figure 1 Effects of 4 weeks of candoxatril 200 mg twice daily on intraocular pressure (IOP) 12 h after the last dose of treatment (n=7). The symbol '2' indicates where data points coincide for two subjects in whom initial IOP was the same and in whom IOP decreased by the same amount with treatment. NEP=neutral endopeptidase 24.11.

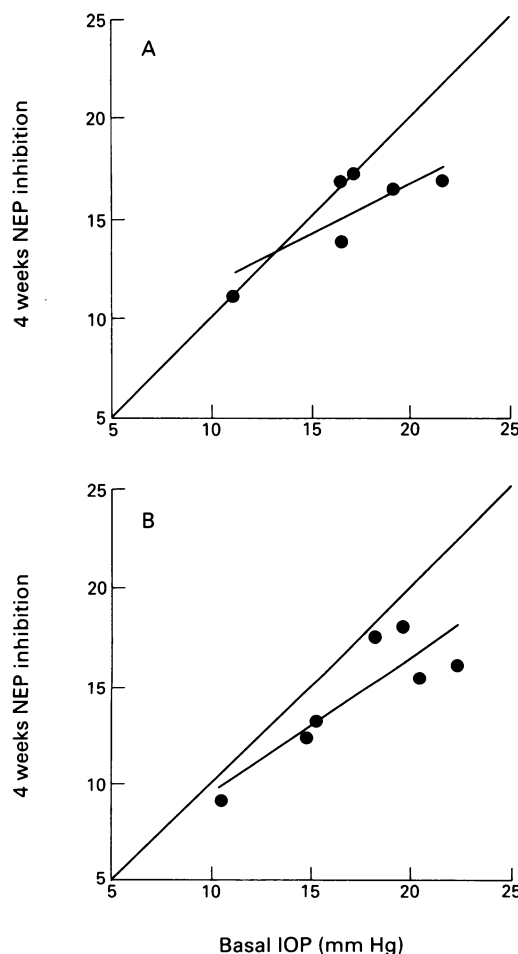
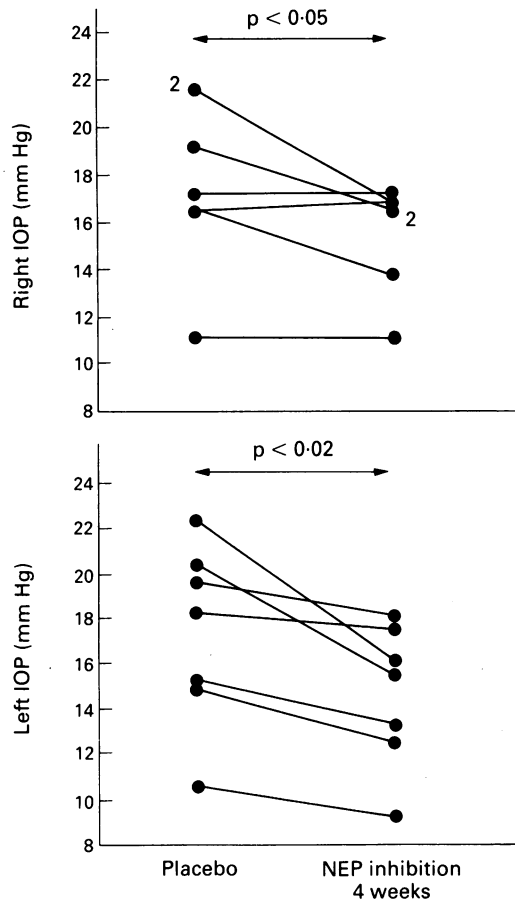


Figure 2 Relation between intraocular pressure (IOP) before treatment and after 4 weeks of neutral endopeptidase (NEP) inhibition 12 hours after the last dose of treatment (n=7). (A) Right eye: $r=0.81$, $p=0.028$, slope=0.51, 95% confidence interval for slope 0.08-0.95. (B) Left eye: $r=0.86$, $p=0.012$, slope=0.68, 95% CI for slope=0.23-1.13. The symbol '2' indicates where data points coincide for two subjects in whom initial IOP was the same and in whom IOP decreased by the same amount with treatment.

USA) with an attached recorder¹⁴ as previously described.¹² Blood samples were obtained after 5 minutes' sitting rest for biochemical analysis including measurement of immunoreactive plasma C-terminal ANP (α hANF 99-126) by radioimmunoassay.¹⁵

Results are given as mean (SE). Mean arterial pressure was calculated as the sum of diastolic pressure and one third of the pulse pressure difference. Single paired comparisons were analysed by two tailed *t* test. The possible acute effects of NEP inhibition were assessed by ANOVA for repeated measurements. Possible relations between variables were assessed by Pearson's correlation analysis and by linear regression analysis. Data were normalised by log transformation before analysis where appropriate.

Results

ACUTE AND CHRONIC EFFECTS OF NEP INHIBITION ON IOP

There was no acute effect of NEP inhibition on IOP in the 6 hours after the first dose of candoxatril (data not shown). After 4 weeks of active treatment with candoxatril, there was a mean reduction in IOP in the right eye of 2.1 (0.8) mm Hg ($p<0.05$ paired *t* test), and in the left eye of 2.8 (0.8) mm Hg ($p<0.02$ paired *t* test). The mean decrease in IOP in the right eye was 11% (4%) and 16% (3%) in the left eye (Fig 1). The fall in IOP with NEP inhibition was greater, the higher the initial IOP (Fig 2). During the placebo controlled washout period, IOP returned towards baseline values in four of the five subjects in which these measurements were obtained (right eye 15 (1) up to 17 (1) mm Hg, left eye 13 (1) up to 15 (1) mm Hg).

EFFECTS OF NEP INHIBITION ON ANP LEVELS AND BLOOD PRESSURE

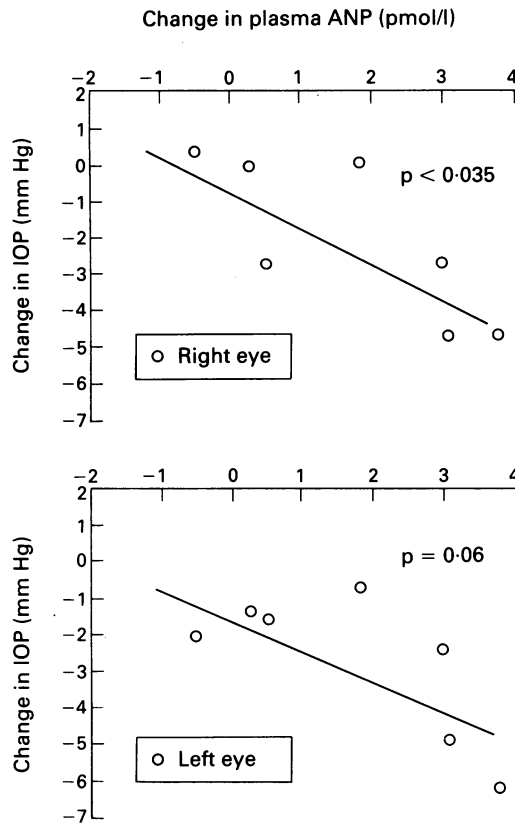
With chronic NEP inhibition there was a rise in plasma ANP from 4.2 (SEM 1.5) to 6.0 (1.5) pmol/l ($p<0.04$) and a significant decrease in mean arterial pressure (119 (4) to 110 (3) mm Hg, $p<0.02$; mean decrease in pulse pressure: 4 (4) mm Hg). The fall in IOP after 4 weeks of NEP inhibition was positively correlated with the increase in endogenous plasma ANP concentration (Fig 3). However, there was no correlation between the decrease in IOP with candoxatril and the change in systemic blood pressure (data not shown).

Discussion

The major finding of our study was that elevation of endogenous ANP within the physiological range by NEP inhibition is associated with a significant reduction in IOP in the normal eye. The observation that the decrease in IOP in the present study was positively correlated with the increase of endogenous ANP levels provides additional evidence that plasma ANP may have an important role in the normal regulation of IOP.

Inhibition of NEP 24.11 affects the meta-

Figure 3 Relation between the rise in plasma atrial natriuretic peptide (ANP) concentration and the decrease of intraocular pressure (IOP) with 4 week neutral endopeptidase (NEP) inhibition (n=7).



bolism of other biologically active peptides including bradykinin, brain natriuretic peptide, and endothelin.¹⁶ However, it is clear that elevation of endogenous ANP levels is a major mechanism for the actions of candoxatril. The increases in plasma ANP and in urinary sodium excretion with candoxatril treatment are similar to those observed in low dose ANP infusion studies.^{17, 18} In addition, candoxatril in normal subjects not only increases both plasma and urinary ANP levels but also increases urinary levels of the second messenger for ANP, cyclic guanosine monophosphate.¹⁹ In the eye, an ANP induced rise of guanylate cyclase has also been described in the ciliary body.⁶

There have been several studies examining the possible relation between systemic blood pressure and intraocular pressure. In the Framingham study, there appeared to be an association with IOP in subjects with systemic hypertension, but not in subjects with blood pressure in the normal range.^{20, 21} Some drugs – for example, carbonic anhydrase inhibitors and β adrenergic blockers, have antihypertensive effects and lower IOP in patients with glaucoma. However, these effects on IOP appear to be related to specific actions of the drugs within the eye rather than to a non-specific response induced by a change in systemic blood pressure. Diuretics with other mechanisms of action – for example, triamterene and ethacrynic acid, do not alter IOP.²² Other classes of antihypertensive treatment have not been well studied. In a previous acute study, high dose intravenous ANP was reported to result in a marked decrease in IOP without a significant change in blood pressure.¹¹ In the present study, in which blood pressure did decrease with chronic NEP inhibi-

tion, there was no clear relation between the changes in IOP and in systemic blood pressure.

Of particular interest in our study was the observation that the decrease in IOP with NEP inhibition was most marked in subjects with high initial IOP, with an average decrease in IOP with treatment of 11 to 16%. In a previous study, Diestelhorst¹¹ reported a similar order of reduction of around 15% in IOP after intravenous injection of pharmacological doses of ANP in patients with pathologically high IOP.

In conclusion, our study suggests that ANP may play an important role in humans in the normal control of intraocular pressure. Furthermore, our results suggest that NEP inhibition may be an important new way in which to manage patients with glaucoma.

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