

# Ocular Hypotension Induced by Electroacupuncture

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## ABSTRACT

The purpose of this study was to investigate the effects of electroacupuncture (EA) on aqueous humor dynamics in rabbits. EA stimulation was performed through two acupuncture needles placed in close proximity to the sciatic nerve. The sites of needle entry were anesthetized. After 1 hr of EA stimulation, intraocular pressure (IOP) decreased and was accompanied by reductions of blood pressure and aqueous humor flow rate. The maximum reduction of IOP was 9 mmHg at 3 hr and decreases in norepinephrine and dopamine levels in aqueous humor occurred simultaneously. In addition, EA stimulation induced an 8-fold increase of endorphin levels in aqueous humor. Ocular hypotension induced by EA lasted for more than 9 hrs and was antagonized by naloxone pretreatment. Furthermore, the EA-induced ocular hypotension was reduced markedly in sympathetically denervated eyes compared with the response of intact, normal eyes. Antagonism of EA-induced ocular hypotension by naloxone, suppression of aqueous humor flow and catecholamine levels by EA and elevation of endorphin levels in aqueous humor by EA indicate that opioids/opiate receptors are involved in modulating ocular hydrodynamics in response to EA.

## INTRODUCTION

Techniques utilized in traditional Chinese medicine have been developed over a period of at least 2,000 years. Archeological finds of the late Shang Dynasty (c. 1000 B.C.) included both acupuncture needles and divination bones on which were inscribed descriptions of medical problems where these implements were utilized. Acupuncture and electroacupuncture (EA) have been used in traditional Chinese medicine to treat a wide range of diseases and conditions (1). Previous studies have shown that acupuncture needling alone and with electric stimulation evoke therapeutic effects in a variety of medical conditions that involve pain, depression, drug addiction, gastrointestinal dysfunction, anxiety, and cerebrovascular accident (2). Other studies have demonstrated that the opioid receptor antagonist, naloxone, reversed EA-induced inhibitory effects on sympathetic cardiovascular responses (3). However, the effects of EA on aqueous humor dynamics, such as intraocular pressure (IOP) and aqueous humor flow, have not been investigated.

Previous studies have demonstrated that the pain relieved by acupuncture was due to the elevation of endorphin levels in the brain (4,5). It is hypothesized that EA-induced IOP-lowering effects

modify aqueous humor flow and neuroendocrine function (beta-endorphin, catecholamines) through the involvement of opioid/opiate receptors. The purpose of this study was to examine the effects of EA on aqueous humor dynamics and determine the underlying mechanism(s) responsible for the ocular hypotension induced by low frequency electrical stimulation.

In this study, experiments investigated: 1) the consequences of EA on IOP, aqueous humor flow rate, and blood pressure; 2) possible antagonism of EA-induced effects on IOP by surgical sympathectomy and by pretreatment with an opioid receptor antagonist, naloxone; and 3) alterations of nor-epinephrine, dopamine and beta-endorphin levels in aqueous humor elicited by EA stimulation.

## MATERIALS AND METHODS

### Animals

New Zealand White rabbits (2.5–4.0 kg) of either sex were utilized in this study. One group of rabbits ( $n = 4$ ) was subjected to unilateral surgical sympathectomy (SX) as described below. After sympathetic denervation, rabbits were allowed to recover for two weeks before further experimentation. Animal care and treatment were in accordance with the resolutions in use of animals for research established by the Association for Research in Vision and Ophthalmology.

### Sympathectomy

In rabbits anesthetized with pentobarbital (30 mg/kg, i. v.), the cervical sympathetic trunk and superior cervical ganglion were isolated surgically and removed unilaterally. The successful isolation was confirmed by stimulating the nerve trunk while observing the dilation of the pupil prior to removal. Subsequently, the right superior cervical ganglion and two millimeters of the postganglionic sympathetic nerve trunk were excised. The superior cervical ganglion remained intact in the left eye to serve as a control. Denervated eyes were tested two weeks after surgery for the lack of response to 1% hydroxyamphetamine, an indirect acting sympathomimetic amine; normally innervated eyes responded with a brisk mydriasis whereas denervated eyes did not respond. Two weeks or more after SX, IOP experiments were performed.

### Electroacupuncture

On the day before the experiments, the thighs of rabbits were shaved. As shown in Figure 1, the acupuncture needle was applied to the designated area of Huantiao (GB30) acupuncture point of the leg. The Huantiao point (lesser-yang gall bladder muscle channel, GB30) was located at the junction of the lateral  $1/3$  and medial  $2/3$  of the distance between the prominence of the great trochanter and the hiatus of the sacrum nearby the sciatic nerve. The designated area was locally anesthetized with 0.5 ml of 2% lidocaine. The sterilized acupuncture needles (34G  $\times$  1.0 in) have been applied to human legs by the authors (Chu and Potter), and there have been no observations of discomfort. In rabbits, sciatic nerves were stimulated with needles connecting to a Grass SD9 stimulator that provided electrical impulses (0.1 to 3 Hz, 0.1 to 1V). During EA, rabbits were restrained gently by hand in a quiet environment. The stimulation period ranged from 0.5 to 1 hr. For the sham IOP experiments, acupuncture needles were inserted without EA stimulation and 2 inches away from the sciatic nerve with EA. After EA or acupuncture, the acupuncture sites showed no signs of inflammation. Rabbits were able to move without discomfort immediately after the experimental procedure. The initial experiments investigated the effects of acupuncture needling (without electrical stimulation) on IOP. Sterilized acupuncture needles were inserted perpendicularly to a depth of 0.8 inch into the leg mus-

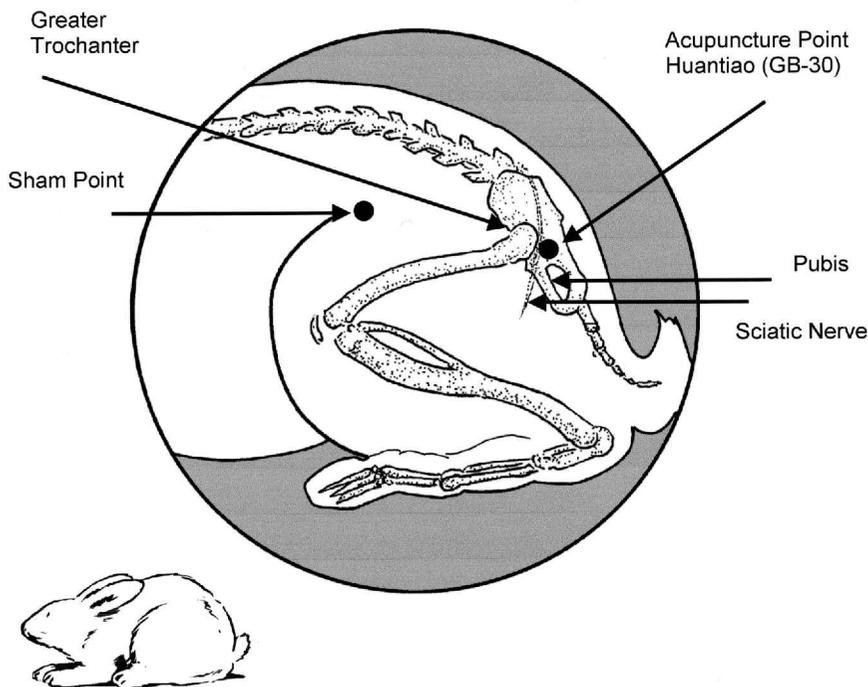


FIGURE 1. Diagram of the location of acupuncture points in the leg of rabbit.

cles of rabbits. After inserting acupuncture needles, they were rotated clockwise one full turn every 20 min for up to one hour.

### Intraocular Pressure Measurements

IOP (mmHg) was measured before and after EA using a calibrated pneumatonometer (Model 30, Mentor Co., Norwell, MA). Tetracaine (0.1%, 25  $\mu$ l) was applied to each cornea before the IOP measurements to minimize discomfort of this procedure. IOP was measured by pneumatonometry in normal ( $n = 4$ ) and surgically denervated rabbits. Two baseline readings were taken at  $-1.0$  and  $0$  hr before EA administration, and post EA determinations of ocular pressures were made at 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 9 hr. At the end of each series of IOP measurements, stability of the tonometry was confirmed using the verifier supplied by the manufacturer. In other experiments, EA's effects on IOP were performed following naloxone (13 mg/kg, i.v.) administration, either pretreatment before EA or at 6 hr after stimulation by EA.

### Blood Pressure Measurements

For these experiments, rabbits were kept in a restrainer. After shaving the ear, a section of the central ear artery was anesthetized locally with 0.5 ml of 2% lidocaine. Subsequently, the central ear artery was cannulated with a 23-gauge butterfly needle connected to a three-way stopcock and pressure transducer (Becton-Dickerson, Franklin Lakes, NJ). This system was filled with heparinized saline (10 units/ml). The Grass polygraph 79D Model (Quincy, MA) and transducer (Statham/Gould, Model P23) were calibrated prior to measuring mean arterial blood pressure. The control mean arterial pressure was initially recorded for 1 hour prior to initiating EA. Immediately after EA, the opposite ear

artery was cannulated with the butterfly, and the mean arterial pressure was again measured continuously for 5 hours.

### Aqueous Humor Flow

This laboratory has shown that the IOP lowering effect of several drugs that inhibit sympatho-adrenal activity is associated with reduction of aqueous humor flow rate (6,7). In this laboratory, aqueous humor flow rates are measured in rabbit eyes using fluorescein dilution as quantified by a Fluorotron Master (Ocumetrics, Palo Alto, CA). The uniform stromal depot method, described previously (8), is used to load fluorescein into the eyes. The general method of fluorometric measurement and calculation of aqueous humor flow rate utilized have been described previously (6,9). In the current set of experiments, basal control recordings of flow rate were established in the first week. The following week rabbits from the same group in which IOP measurements were performed with EA application, and flow rates in both eyes were determined. Fluorometric recordings started at -1, 0 hr before EA administration, and subsequent recordings were made at 1 hr intervals for a period of 4 hr.

### Norepinephrine and Dopamine Levels in Aqueous Humor

Removal of aqueous humor samples from rabbits by paracentesis has been described previously (10). Prior to the paracentesis procedure, groups of rabbits were subjected to 1 hr-EA and then sacrificed rapidly with an overdose of sodium pentobarbital at the appropriate times. A clean, previously autoclaved Hamilton microliter syringe and a 30-gauge  $\times$  2 inch needle were used for aspiration of aqueous humor. Aqueous humor samples were removed by paracentesis at 0 (control) hr and at 1, 2 and 3 hr (after EA application), respectively. Four groups of rabbits were used including one group ( $n = 6$ ) for the determination of basal levels (0 hr) and three groups ( $n = 4$ ) for time-related responses (1 hr, 2 hr, 3 hr) to EA administration. Samples of aqueous humor were immediately treated with  $\text{HClO}_4$  (pH 3.0) and centrifuged for 10 min at 20,000g. Supernatants were stored in the vials at  $-85^\circ\text{C}$  until 25  $\mu\text{l}$  aliquots were analyzed by injection into a high performance liquid chromatography with electrochemical detection system (Model 5500, ESA, Inc., Chelmsford, MA). Solutions of norepinephrine and dopamine were freshly prepared as standards for each experiment. The peaks of norepinephrine and dopamine from samples were quantified by comparison to the known standards.

### Beta-endorphin Levels in Aqueous Humor

After EA application, four groups of rabbits ( $n = 4/\text{group}$ ) were sacrificed with an overdose of sodium pentobarbital. The aqueous humor samples were removed by paracentesis immediately at 0 (control) hr and at 1, 2 and 5 hr, respectively. The sample of aqueous humor was quickly transferred to a small vial containing aprotinin and placed in ice. The levels of beta-endorphin in aqueous humor were quantified utilizing a peptide enzyme immunoassay kit (Peninsula Lab., Inc. San Carlos, CA). The concentrations of beta-endorphin in the aqueous humor samples from this study were within the concentrations of the standard curve (range: 0.04 to 25 ng/ml). The data in these experiments were replicated four times using duplicate samples.

### Chemicals

Naloxone was obtained from RBI (Natick, MA). All other chemicals used in this study were obtained from Sigma Chemical Co. (St. Louis, MO). Naloxone, a nonselective opioid receptor antago-

nist, was utilized initially to determine the possible role of endogenous opioids in EA-induced ocular hypotension.

### Statistical Analysis

The statistical comparisons of EA-induced changes were made utilizing an analysis of variance for multiple group comparisons followed by a Student-Newman-Keuls test (Instat program, Graph-Pad Software, San Diego, CA). The levels of significance were chosen as  $p < 0.05$ . For data presented in graphs and table from experiments, means  $\pm$  S.E were calculated from multiple determinations.

## RESULTS

### Intraocular Pressure

Initially, the effects of acupuncture without electrical stimulation on IOP were investigated. After inserting acupuncture needles up to one hour, there was appreciable change of  $3.8 \pm 0.6$  mmHg in IOP at 2 hr ( $n = 4$ ). In sham experiments, acupuncture needles inserted away from sciatic nerve produced no change in IOP. However, with EA (3 Hz, 1V) stimulation for  $1/2$  hr, the maximum reduction of IOP with  $1/2$  hr-EA was 5 mmHg at 2 hr. Subsequently, IOP returned slowly to the control value. Furthermore, as shown in Fig. 2, 1-hr electrical stimulation (3 Hz, 1V) through two acupuncture needles caused an immediate, bilateral decrease in IOP of 6.5 mmHg. The maximum reduction

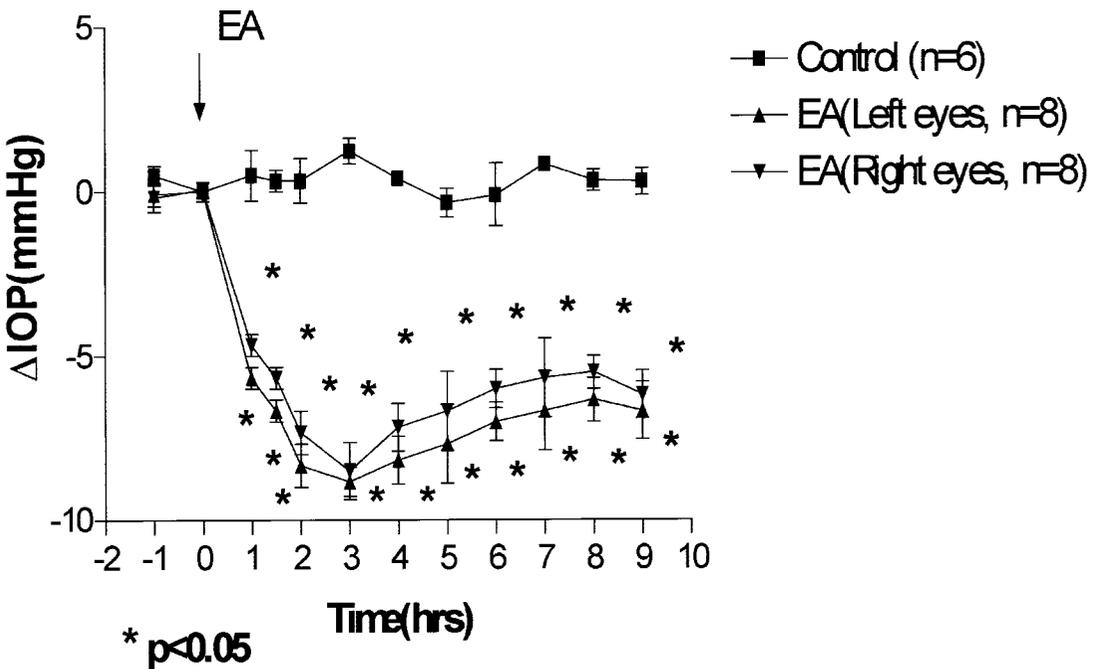


FIGURE 2. One-hour low frequency electroacupuncture (EA, 3Hz, 1V) induces the intraocular pressure (IOP)-lowering effects of normal left and right eyes of normal New Zealand white rabbits. The average of control IOP was  $21 \pm 1.5$  mmHg. \* $p < 0.05$ , Significantly different from the control.

of IOP following 1-hr EA was 9 mmHg after EA at 3 hr. The ocular hypotension induced by 1 hr EA lasted for approximately 9 hr. There was no significant change in pupil diameter caused by EA stimulation.

Aqueous Humor Flow Rate

The purpose of the aqueous flow rate experiments was to identify the potential mechanism(s) for the EA-induced ocular hypotension. In previous studies in this laboratory, the mechanism(s) of IOP lowering effects of various drugs, including bremsazocine (a kappa opioid receptor agonist), have been demonstrated to be accompanied by reduction in rates of aqueous humor inflow (6,7,11). As shown in Figure 3, basal (control) measurements of aqueous humor flow in normal rabbits ranged between 2.0 and 2.5  $\mu$ l/min. After 1 hr-EA by the acupuncture needles, there were bilateral decreases in IOP accompanied by reductions of aqueous humor flow rates by 42%. However, the effect of EA on aqueous humor flow rate was transient compared to the effect of EA on IOP. The aqueous flow rates gradually returned to the control level but preceded that of the IOP recovery.

Role of Sympathetic Nervous System

Changes in neuroendocrine function within the eye could be involved in the EA-induced suppression of ocular hydrodynamics. Therefore, the changes in IOP by EA for one hour were studied in the sympathetically denervated rabbit eyes. In unilaterally denervated rabbits, the EA-induced ocular hypotension was significantly less in the denervated eye compared with the intact, normal eye (Fig. 4). Therefore, it is suggested that EA-induced ocular hypotension may be mediated, in part, through suppressed activity of the sympathetic nervous system.

To confirm that neurotransmitter release from sympathetic nerves of the ciliary body is modulated by EA stimulation, the levels of norepinephrine and dopamine in aqueous humor were quanti-

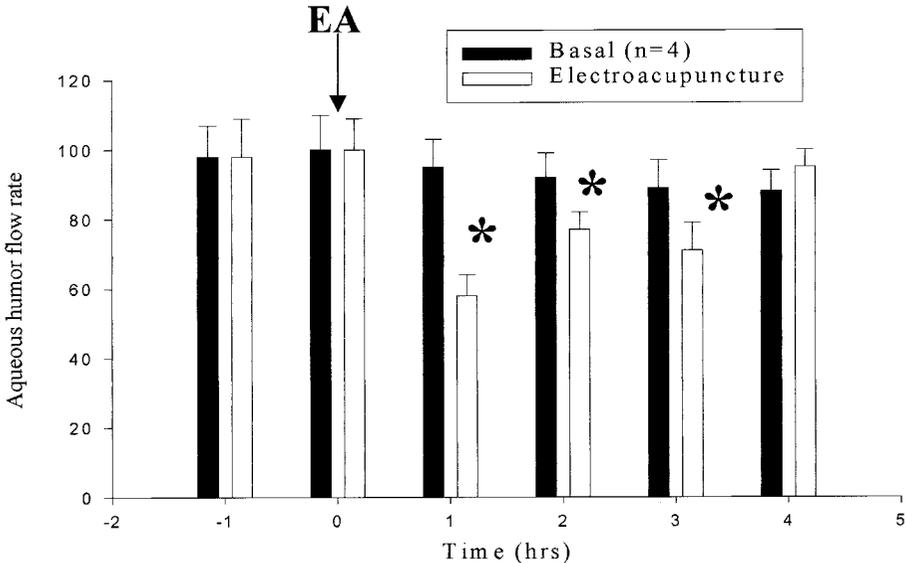


FIGURE 3. Reduction of aqueous humor flow rates (AHFR) by electroacupuncture (1 hr EA) in normal rabbits. The average of basal rate of aqueous humor flow was  $2.3 \pm 0.3 \mu$ l/min (n = 4).  $p < 0.05$ , Significantly different from the basal.

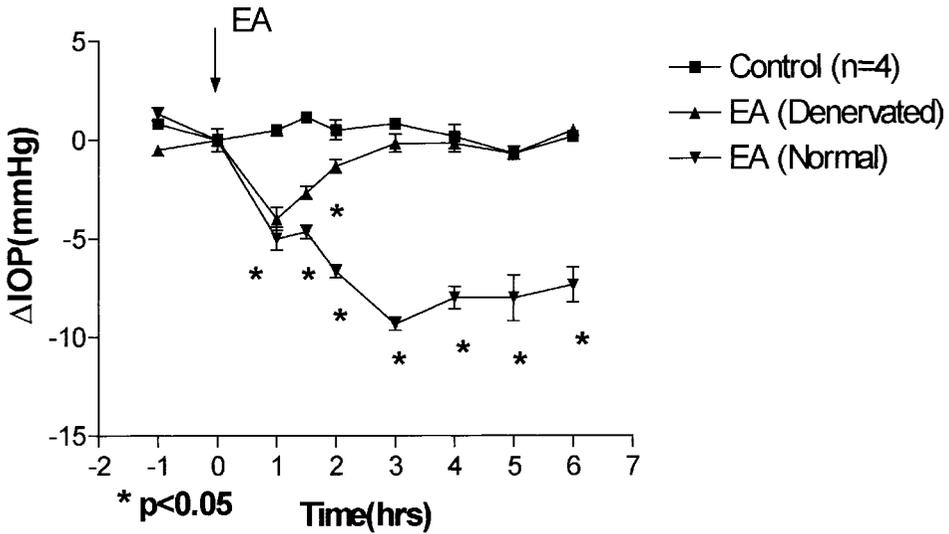


FIGURE 4. The effects of electroacupuncture (EA) on intraocular pressure (IOP) of normal and sympathetically denervated eyes of rabbits. \* $p < 0.05$ , Significantly different from the control.

fied. The results showed that EA-induced ocular hypotension was associated with the suppression of aqueous levels of norepinephrine and dopamine. As shown in Figure 5A and 5B, at 2 hr post EA, the maximum reduction in IOP (9 mmHg) occurred along with decreases in the levels of norepinephrine and dopamine in aqueous humor (60% and 40%, respectively). However, the levels of norepinephrine and dopamine returned to control levels at 3 hr post EA stimulation even though the IOP remained reduced.

#### Role of Opioid Receptors in EA-induced Changes in Ocular Hydrodynamics

Previous studies showed that high doses of naloxone (10–15 mg/kg), a nonspecific opioid receptor antagonist, reversed completely reduction of blood pressure induced by EA (12). Further experiments were performed in the present study to determine whether opioid receptors were involved in EA-induced IOP-lowering effect utilizing the opioid receptor antagonist, naloxone. Based upon previous studies (12), the mid-range dose of naloxone was utilized to ascertain antagonism of ocular hypotension induced by EA. There was no change in IOP caused by i.v. naloxone alone. In contrast, EA-induced ocular hypotension was antagonized by naloxone (13 mg/kg, i.v., Fig. 6).

Furthermore, to confirm whether beta-endorphin release played a role in the ocular hypotension induced by EA stimulation, the aqueous humor levels of endorphin were determined by immunoassay. As shown in Table 1, basal levels of endorphin in aqueous humor of rabbit were 0.85 ng/ml. Effects of EA stimulation caused an increase of endorphin levels from 0.85 to 1.85 and 7.5 ng/ml at 1 hr and 2 hr, respectively. Furthermore, EA caused sustained increase of endorphin levels from 0.85 (control) to 5 ng/ml at post-EA of 5 hr; at this time after EA, the IOP was reduced by 5 mmHg.

#### Arterial Blood Pressure Changes by EA

Previous studies reported that acupuncture needling induced lowering of blood pressure in hypertensive rats (13) and humans (14). In this study, the effects of EA on mean arterial blood pressure

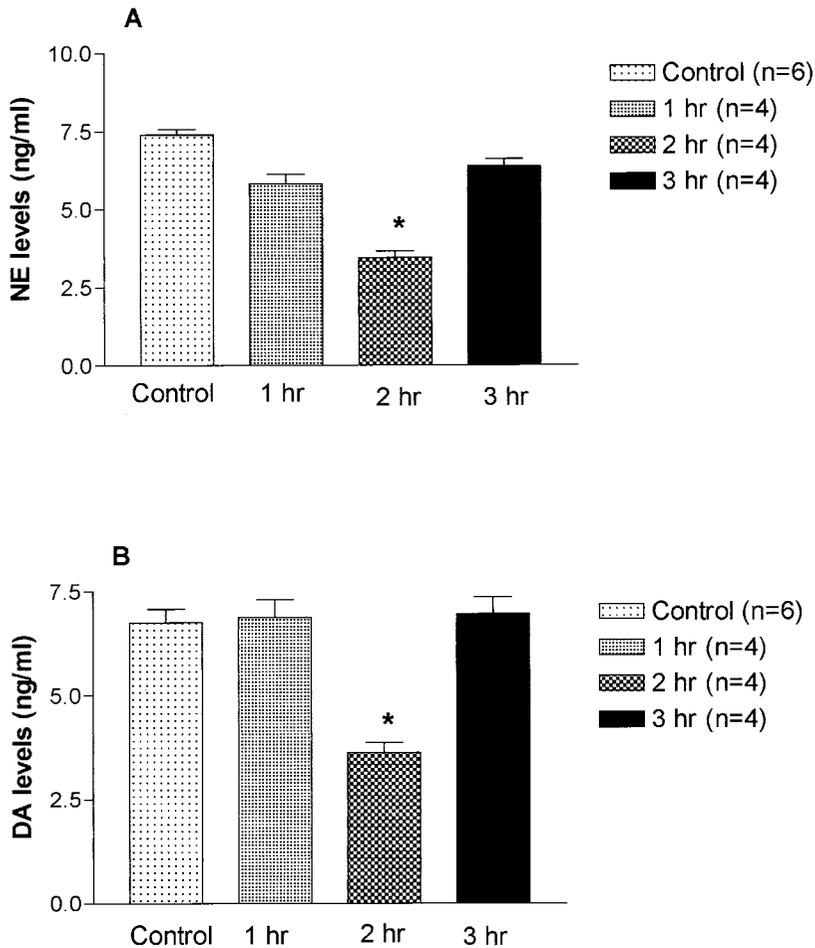


FIGURE 5. Electroacupuncture (EA)-induced alteration of aqueous norepinephrine (NE, Panel A) and dopamine (DA, Panel B) levels in normal rabbits, \* $p < 0.05$ , Significantly different from the control.

were investigated in normal, unanesthetized rabbits. As shown in Table 1, EA caused substantial declines of arterial pressure but the effect was more transient than the effect on IOP. Subsequently, arterial pressure returned slowly to the new baseline 5 mmHg below the control value at 6 hr. The maximum reduction of mean arterial blood pressure was 28 mmHg after 1 hr-EA. There was no difference of EA-induced arterial hypotension between normal and denervated rabbits.

### DISCUSSION

Recently, acupuncture has been evaluated by both clinicians and biomedical scientists because of a renewed interest in techniques utilized in complementary/alternative medicine. Based upon these observations, it was of interest to determine if acupuncture could induce changes in ocular hydrodynamics.

Moreover, it has been shown that exercise can induce ocular hypotension (15), but the mechanism(s) producing this effect is (are) not understood. Because EA can induce certain neuroendocrine

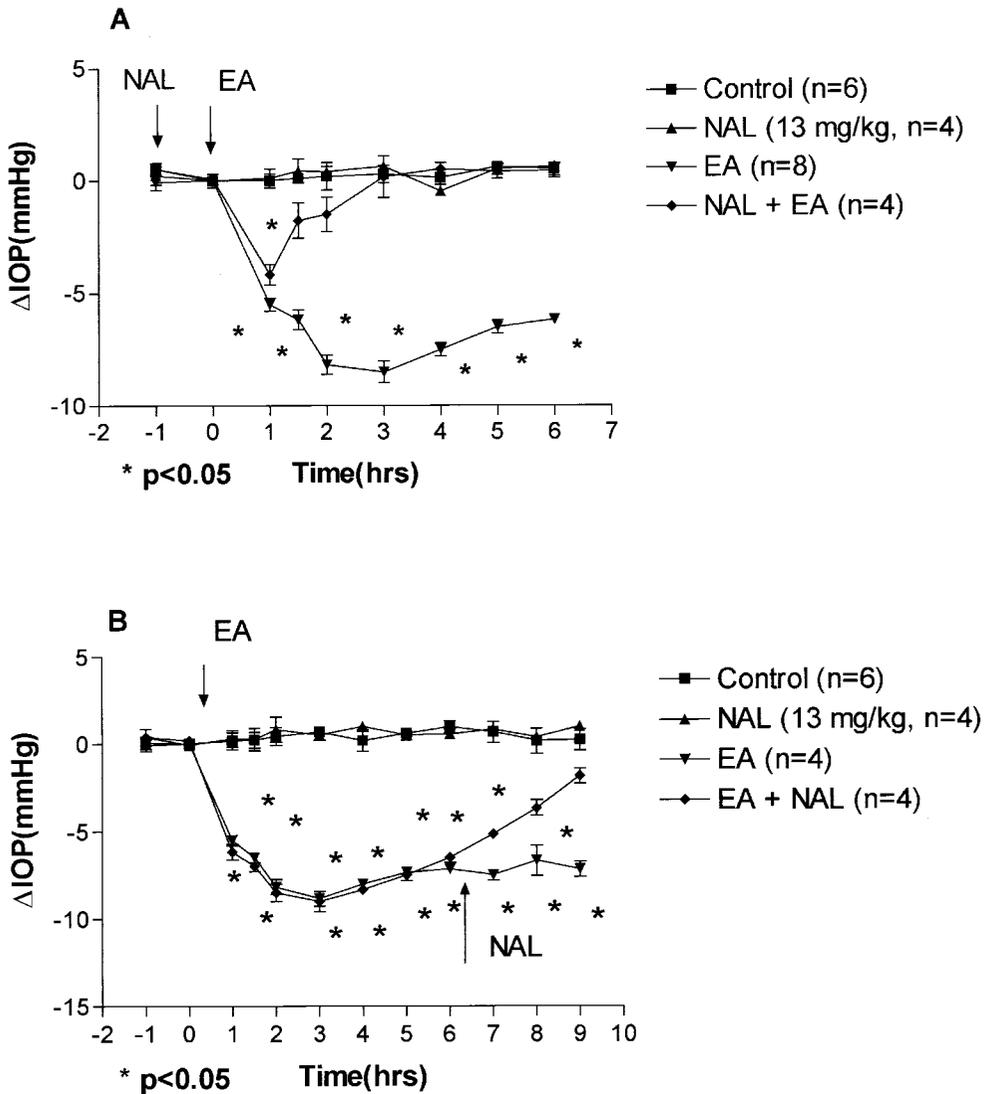


FIGURE 6. Naloxone (NAL, 13 mg/kg, iv) pretreatment (panel A) and injection after (panel B) reverse electroacupuncture (EA) induced ocular hypotension in normal, conscious rabbits. \* $p < 0.05$ , Significantly different from the control.

aspects of exercise, this study was performed to determine whether alterations of IOP could occur as a result of activating the sciatic nerves. In preliminary experiments, there were minimal changes in IOP by applying traditional acupuncture needling techniques, including rotating, lifting and thrusting, in the thigh muscles of rabbits. The intent of EA stimulation was to increase the afferent nerve activity by electrically stimulating the sciatic nerves through acupuncture needles. After EA stimulation for  $1/2$  hr, significant changes of IOP were induced, but the effect lasted for only 3 hr. However, with 1 hr of EA, substantial and more sustained depression of IOP was produced. To our knowledge, this is the first report that EA stimulation causes a bilateral decrease in IOP of normal, conscious rabbits. Moreover, this study demonstrates that lowering of IOP can be elicited by a minimally invasive procedure that depresses sympathoadrenal activity and raises beta-endorphin levels. Therefore, it is important to determine in greater detail the potential mechanisms by which EA stimulation lowers IOP.

TABLE 1.

Effects of electroacupuncture (EA) stimulation on intraocular pressure, mean arterial blood pressure and aqueous endorphin levels in normal rabbit eyes

	Intraocular pressure (mmHg)	Arterial pressure (mmHg)	Endorphin (ng/ml)
Normal	21.5 ± 2.4	93 ± 13	0.85 ± 1.5
EA			
1 hr	15.3 ± 1.6*	65 ± 15*	1.75 ± 0.9*
2 hr	13.2 ± 2.1*	75 ± 16	7.50 ± 1.5*
5 hr	16.5 ± 2.2*	79 ± 18	5.10 ± 1.6*

Value are expressed as mean ± S.E. (n=4). \*p < 0.05, Significantly different from normal.

The traditional acupuncture point "Huantiao (GB 30)" that was used in the present study was chosen because it offered more consistency and greater precision in terms of needle placement. The placement of the needles is as important in electrical stimulation as in manual manipulation. Although the electric current spreads out from the needle, electrical stimulation of non-acupuncture points in sham experiments produced less ocular hypotensive effects (data not shown). Future experiments will be required to confirm the conditions under which the reduction of IOP is related to the specific acupuncture point (Huantiao, GB30) and other points.

A previous report has demonstrated a depressor effect on blood pressure induced by acupuncture stimulation in anesthetized rabbits (16). Thus, it is of interest to identify other changes in bodily function that are influenced by acupuncture. Results from this study suggest that lowering of IOP by EA stimulation is associated with reduction of blood pressure in normal, conscious rabbits. Further studies demonstrated the suppression of the rate of aqueous humor flow. As noted, when EA stimulation lowered IOP, a reduction of aqueous humor flow rate occurred during the early time periods. Therefore, the ocular hypotension induced by EA stimulation in the late stages are most likely due to factors other than the change in formation rate of aqueous humor. Thus, other factors, such as enhanced outflow facility, may contribute to the ocular hypotensive effects at later time periods. It is possible that outflow facility increases in response to elevated levels of beta-endorphin. Future studies will be required to investigate if EA stimulation enhances outflow facility in response to the elevation of endogenous opioid levels in aqueous humor.

To confirm involvement of sympathetic nerves in the ocular action of EA, unilateral sympathectomies of rabbit eyes were performed. EA-induced ocular hypotension was reduced markedly in the denervated eye compared with the intact, normal eye. Results from these experiments supported the postulated requirement of intact sympathetic innervation in the early action of EA on ocular hydrodynamics. However, these denervation experiments did not provide detailed information concerning the level of involvement of the opioidergic system.

In humans, it has been shown that catecholamine levels are decreased by EA (17). Because previous studies have also shown that reduction of aqueous norepinephrine levels contributes to lowering of IOP by prejunctionally active agents (18), norepinephrine and dopamine levels were studied to correlate the IOP-lowering effects with other actions evoked by EA stimulation. Previous experiments with delta and kappa opioid receptor agonists have demonstrated that opioid receptor activation depresses sympathetic nerve activity in the iris-ciliary body (11,19). Present results demonstrated that EA-induced ocular hypotension was associated with the suppression of aqueous norepinephrine and dopamine levels at early time periods when aqueous flow rates were depressed. Thus, it is suggested that changes in endorphin levels, rather than norepinephrine and

dopamine levels in aqueous humor probably account for the late-occurring ocular hypotensive action of EA stimulation.

It has been demonstrated that naloxone (10–15 mg/kg), an opioid receptor antagonist, reversed completely the depressor response of blood pressure induced by EA in rats (12). Other studies showed that EA-induced analgesia was associated with an increased endorphin activity in the brain, and this analgesic effect was reversed by naloxone (20). Results in the current experiments showed that naloxone reversed EA-induced ocular hypotension. Based on current findings with naloxone, it is indicated that multiple subtypes of opioid receptors may be involved in the IOP-lowering effects induced by EA. Currently, experiments are in progress to determine whether mu, delta, kappa or other receptors are involved in EA-induced ocular hypotension.

Other investigations showed evidence that  $\beta$ -endorphins and enkephalins in the brain play a role in the EA-related modulation of cardiovascular reflex responses (2,21). A report of MRI studies has shown the correlation between acupuncture points and stimulation of the eye with the corresponding activity in the brain associated with visual function (22). This study is the first report demonstrating that the reduction of IOP by EA is correlated with an increase of endorphin levels in aqueous humor. Thus, current results indicate that endorphin release could account for part of the ocular hypotension caused by EA stimulation. This could be especially true in the case of the latter stages of the ocular hypotension induced by EA.

From the data presented, it is concluded that endogenous opioids and opioidergic receptors are involved in the bilateral aqueous humor dynamics and blood pressure responses induced by EA. The presumed mechanisms of action of EA involve increased endorphin levels and reduced norepinephrine and dopamine levels in aqueous humor. Based upon the current studies in rabbits, the potential application of acupuncture as an adjuvant treatment of glaucoma is suggested. Because acupuncture treatment is well accepted by humans for therapy of a variety of diseases, this approach may offer an additional tool for the treatment of glaucoma especially for those patients intolerant of certain glaucoma medications. However, further investigations are required to determine the value and efficacy of acupuncture in humans.

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