Effect of oculomotor nerve stimulation on outflow facility and pupil diameter in a monkey (Cercopithecus ethiops)

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Aqueous humor outflow resistance was studied in monkeys (Cercopithecus ethiops) with intact oculomotor nerves, after the nerve had been severed on one side, and during electrical stimulation of the severed nerve. Pupil diameters (on both eyes) and outflow resistance on the nonstimulated side acted as controls. It was found that the outflow resistance increased and the pupil dilated when the nerve was cut. During stimulation with 2 per second and 20 per second the pupil constricted and outflow resistance decreased, especially so with the high stimulation frequency. Thus in the oculomotor nerve of the monkey there are fibers present which facilitate aqueous humor outflow.

Key words: oculomotor nerve, electric stimulation, aqueous humor outflow resistance, pupil dilatation, pupil constriction, intraocular pressure change, monkeys.

There is a general agreement that cholinergic receptors in the anterior parts of the eye facilitate aqueous humor outflow. This is known from many pharmacological experiments and a massive therapeutic experience. However, only a few investigators have been concerned about the effect on aqueous humor dynamics seen when cholinergic nerves to the eye are stimulated.

Greaves and Perkins[1] stimulated the cut oculomotor nerve of rabbits and found no change in intraocular pressure if extraocular muscle contractions were eliminated. On the other hand, Armaly[2] found a reduction in intraocular pressure and an increase in outflow facility during stimulation of the ciliary ganglion of the cat. Recently, Jampel and Mindel[3] reported that no change in eye pressure was seen on stimulation of the midbrain accommodation center of macaques though a steady accommodation was seen. In the experiments to be reported the problem was studied in the vervet monkey by means of electrical stimulation of the intracranial part of the oculomotor nerve and simultaneous recording of outflow resistance. As pupil responses during oculomotor nerve stimulation have not earlier been studied in monkeys these results are also given.

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Materials and methods

Six vervet monkeys *(Cercopithecus ethiops)* weighing 3.0 to 5.5 kilograms and of both sexes were used. The animals were anesthetized with pentobarbital, 30 mg. per kilogram intravenously. A polyethylene tubing was introduced into the femoral artery and the blood pressure was recorded by means of a pressure transducer. To reach one of the oculomotor nerves (always the left), skin and muscles were reflected off the cranium. Large parts of the parietal and temporal bones were resected. The left hemisphere was elevated with a speculum to expose the oculomotor nerve. The nerve was later cut close to its origin from the brain. Measurements of aqueous humor outflow resistance and of pupil diameter were performed on both eyes (1) with intact oculomotor nerve, (2) after the nerve had been cut on the left side, and (3) during and after stimulation of the cut nerve. Stimulation was performed by applying two silver electrodes to the nerve. Except for the tips, the electrodes were coated with polyethylene and for further insulation warm liquid paraffin was used. The electrodes were connected to a square wave stimulator (H 44, C. F. Palmer Ltd., London).

In all animals stimulation frequencies of 2 and 20 stimuli per second were used. Sometimes a frequency of 50 per second was used, but such an intense stimulation damaged the nerve after a minute or two. The voltage and the duration of each impulse were always the same (50 volts, 1 msec.). From similar experiments where accommodation was studied during oculomotor stimulations, 50 volts were found to be well supramaximal.[4] Pupil measurements were performed with a pair of vernier calipers. Measurements of aqueous humor outflow resistance were performed according to the technique described by Bárány.[5, 6] By this technique outflow resistance values and the successive means of these can be calculated.

Two successive mean values of resistance were obtained during each phase of the experiments (before the nerve was cut; after the nerve was cut; during stimulations; and after stimulations). Also the intraocular pressure at zero infusion rate (P_0) could be extrapolated during the different phases of an experiment and was averaged according to Bárány.[5]

Eyeball movements as the result of oculomotor stimulation were expected to cause trouble, but this was not the case. Only a small adduction occurred when the nerve was stimulated, and these movements did not affect the steady state tracings of the recorder.

Results

The blood pressure was recorded in every monkey and was found to be very steady during the experiments (around 80

Table I. Mean outflow resistance (mm. Hg, minutes per microliter) in 6 monkeys before and after the oculomotor nerve was cut on one side and during electrical stimulation of the cut nerve*

Monkey No.	Oculomotor nerve intact	Oculomotor nerve severed: No stim.	Stim. 2/sec.	Stim. 20/sec.
1				
Expt.	3.87	4.87	4.24	0.77
Contr.	3.17	3.68	3.58	1.64
2				
Expt.	2.92	3.19	2.13	1.07
Contr.	1.92	1.95	1.31	1.45
3				
Expt.	3.50	3.80	3.81	2.44
Contr.	3.19	3.53	4.15	3.66
4				
Expt.	2.01	3.59	2.50	1.73
Contr.	2.17	2.64	2.95	1.89
5				
Expt.	2.31	2.92	2.24	0.81
Contr.	2.49	2.11	1.38	0.96
6				
Expt.	3.25	4.66	3.03	2.47
Contr.	2.74	4.02	3.41	2.59

*One eye acted as control. The values given are the average of the two successive means obtained during each phase of an experiment.

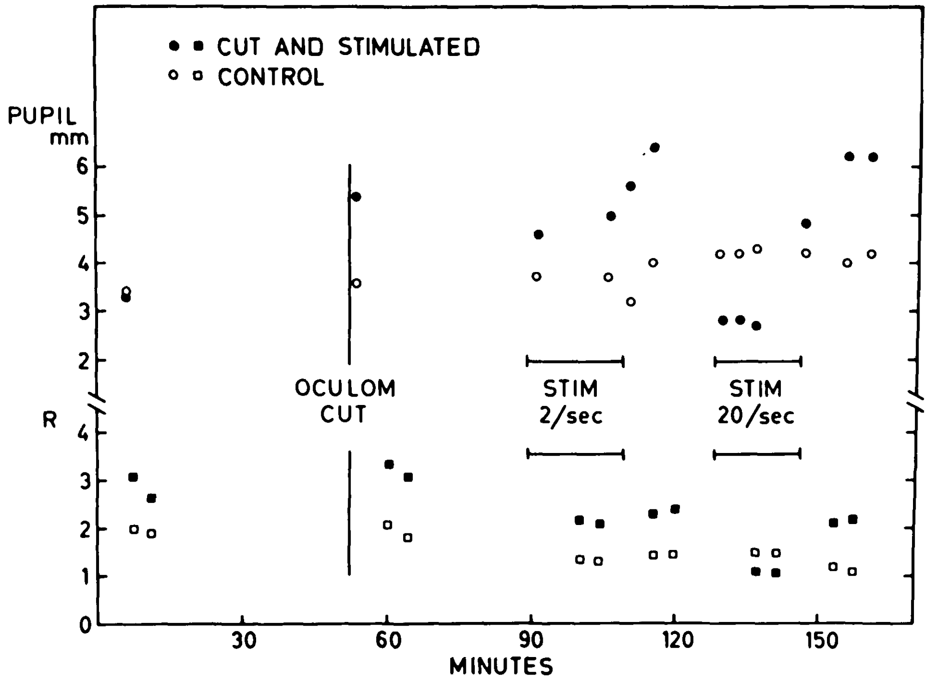

Fig. 1. A typical experiment (monkey 2 of Tables I and II). Pupil diameter and outflow resistance (R) were measured on both eyes of a vervet monkey (3 Kg.) with intact oculomotor nerve, after the nerve had been cut on one side and during and after stimulations of the cut nerve. Black signs indicate experimental eye (cut and stimulated) and clear signs indicate control eye. Each pupil sign (circle) refers to a mean of four individual readings. Each resistance value (square) refers to a successive mean.

to 100 mm. Hg). Also at the start and the end of stimulation periods only small and shortlived changes of the blood pressure occurred. The changes in intraocular pressure (P_0) due to the cutting and later stimulation of the oculomotor nerve were the following. In two monkeys no pressure change (compared with the control eye) occurred after nerve cutting. In three others there was a slight rise and in one monkey a slight decrease of P_0. Stimulation of the cut nerve with 20 stimuli per second increased P_0 by a few millimeters of mercury in three monkeys, left it unchanged in one, and decreased it by a few millimeters of mercury in two monkeys. Thus the P_0 changes were inconsistent. However, the apparatus is not designed mainly for estimating P_0, but for measuring outflow resistance.

Changes in outflow resistance when severing the oculomotor nerve and during stimulations are seen in Table I and in Figs. 1 and 2; Fig. 1 illustrates a typical experiment. It is evident (Table I) that resistance on the control side is not quite stable. Therefore all changes in the experimental eye are compared with those that occur spontaneously on the control side and the resistance differences (experimental eye minus control) for each monkey are plotted in Fig. 2.

In five out of six monkeys there was a distinct rise in outflow resistance (compared to the control side) when the nerve was cut and in one monkey (No. 3 of Table I) a small, insignificant decrease occurred. It is true that in five monkeys the resistance of the control side increased too, but in four of these the resistance increase was larger in the experimental eye.

When the cut nerve was stimulated resistance decreased, especially so with the higher stimulation frequency. It is obvious

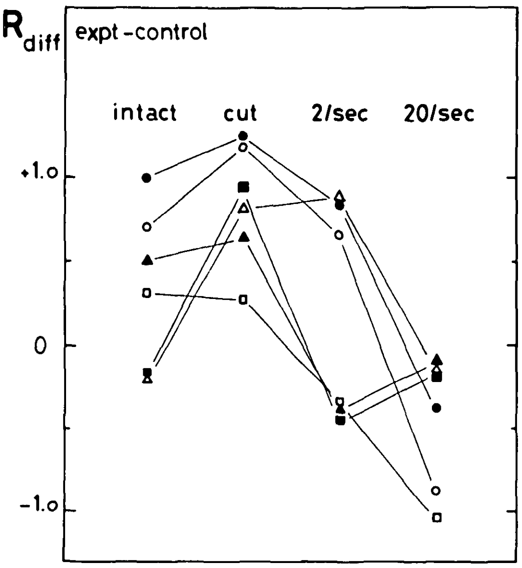

Fig. 2. Difference in outflow resistance (experiment minus control value of each monkey) during the four main experimental stages: intact oculomotor nerve, nerve cut, and the cut nerve stimulated with 2 and 20 stimuli per second. Each animal is designated by one symbol. The abscissa is out of scale and the values are arbitrarily grouped together at the four stages because all experiments did not take exactly the same time.

from Fig. 2 that in five of the six animals 2 stimuli per second caused a decrease in resistance (compare values of cut, unstimulated nerve with those of 2 stimuli per second). When 20 stimuli per second were given there was a considerably greater decrease in resistance in all the experimental eyes than in the controls. Again, most controls showed a decrease in resistance too, but with 20 stimuli per second the decrease was always greater on the experimental side. There was a distinct widening of the pupil in all monkeys when the nerve was cut (Table II). Two stimuli per second to the oculomotor nerve gave a slight pupil constriction in all monkeys, but only once great enough to give the same diameter as when the nerve was unsevered. Twenty stimuli per second gave a pupil diameter of approximately the same size as in the unsevered nerve (No. 3 and No. 4 in Table II) or smaller (four experiments).

Discussion

The present experiments have shown that cutting the preganglionic portion of the oculomotor nerve gives an increase in outflow resistance and widens the pupil. Stimulation of the distal portion of the cut oculomotor nerve gives pupil constriction and a decrease in outflow resistance. Intraocular pressure changes as a result of severing or stimulation of the nerve were not consistent.

The pupil changes on cutting and on stimulation were immediate, i.e., the response was seen within one second. How rapid the outflow effects were could not be estimated, because the constant pressure infusion technique used for outflow measuring did not give the first value until 4 minutes after nerve cutting or the beginning of stimulation (values refer to steady state), and did not give the first averaged value until after another 4 minutes.

The effect of cutting the nerve clearly shows that there is a tonus in the nerve of the pentobarbital-anesthetized monkey. However, it cannot be predicted from the present results that this is the case also in physiologically sleeping monkeys.

An interesting question in nerve stimulation experiments is the frequency-response correlation. Very few such investigations have been done, especially on parasympathetic nerves: 25 to 30 stimuli per second gave maximal effects on salivary glands and 25 stimuli per second gave maximal iris contraction in the cat.[8] The only investigation in monkeys on the stimulation frequency-response correlation in parasympathetic nerves has shown that maximal accommodation effects are reached when the oculomotor nerve is given 20 to 50 stimuli per second.[4] The stimulation frequency giving maximal outflow response could not be estimated in the present investigation for technical reasons but obviously a distinct outflow response is obtained with a stimulation frequency (20 per second) that also produces a clear-cut accommodation.[4]

Table II. Pupil diameters (mm.) in 6 monkeys before and after the oculomotor nerve was cut on one side and during electrical stimulation of the cut nerve*

Monkey No.	Oculomotor nerve intact	Oculomotor nerve severed		
		No stim.	Stim. 2/sec.	Stim. 20/sec.
1				
Expt.	3.2	5.3	3.2	2.2
Contr.	3.1	2.9	5.5	4.5
2				
Expt.	3.3	5.4	4.8	2.8
Contr.	3.4	3.6	3.7	4.2
3				
Expt.	2.9	5.2	4.3	2.5
Contr.	2.9	2.8	2.8	2.6
4				
Expt.	3.1	5.1	5.0	3.1
Contr.	3.1	2.7	3.0	2.9
5				
Expt.	2.8	4.7	3.4	2.2
Contr.	3.0	3.2	3.5	3.5
6				
Expt.	2.4	5.2	3.7	2.0
Contr.	2.5	2.5	2.6	2.7

*One eye acted as control. The values given are the average of several (at least 4) individual readings during each phase of an experiment.

The increase in stimulation frequency from 2 to 20 per second gave a very distinct decrease in pupil diameter. However, the miosis caused by 20 per second could not be considered maximal in view of the extreme miosis (1.5 mm. and less) seen after pharmacological stimulation.[9, 10] It is therefore likely that neither maximal accommodation[4] nor maximal miosis is reached with 20 stimuli per second.

Jampel and Mindel[3] in their refined stimulation experiments in monkeys found no change in eye pressure when they induced accommodation by midbrain stimulation. Besides, in a single experiment the pressure decay curve was not influenced by midbrain-induced accommodation. As long as there is no evidence for separate brain centers for accommodation and outflow resistance, their results seem to be in conflict with those of the present investigation. On the other hand, the present results agree with those found by Armaly[2] on cats.

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