The nucleus for accommodation in the midbrain of the macaque

The effect of accommodation, pupillary constriction, and extraocular muscle contraction produced by stimulation of the oculomotor nucleus on the intraocular pressure

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This paper reports upon: (1) the relationship between iris-bulge and accommodation of the eye; (2) the stereotaxic localization of midbrain sites that produce iris-bulge and changes in the retinoscopic reflex (accommodation); (3) the patterns of response from excitation of sites within the oculomotor nuclear complex; and (4) the effect of stimulation of the parasympathetic nucleus on the intraocular pressure.

I t has been generally accepted, in spite of many decades of controversy, that the nuclei for the intraocular muscles are located in the anterior and dorsal region of the oculomotor complex, probably in the small-celled nuclei. The first description of the autonomic component of the oculomotor nucleus was by Edinger and Westphal and bears their names. It consists of a paired column of relatively small nerve cells, extending anteriorly from about the middle of the oculomotor complex, dorsal and medial to the somatic cell columns. A rostral extension of these small cell groups lies close to the midline, anterior and dorsal to the most rostral somatic oculomotor subnucleus. This extension gives the appearance of a single median nucleus and has been called the “rostral median nucleus,” the “anteromedian nucleus,” or the “rostral part of the Edinger-Westphal nucleus.” There has been some uncertainty in regard to whether the Edinger-Westphal nucleus and the anteromedian nucleus are two separate distinct nuclei or represent a continuous cell mass.

Electrical stimulation experiments with histological verification have proved that the Edinger-Westphal nucleus was actually part of the visceral efferent component. Pupillary constriction has served as the main functional indicator and was obtained...
by stimulation of both the body and rostral parts of the Edinger-Westphal nucleus. However, there have been no recent detailed studies of the functional representation of accommodation in the parasympathetic component and the literature on this subject is meager. Hensen and Volckers produced pupillary constriction and forward bulging of the iris that was due to lens movements from stimulating the floor of the third ventricle of the dog. They localized accommodation in the most rostral part of the oculomotor complex. Adamiik confirmed these observations. Bender and Weinstein evoked conspicuous bilateral bulging forward of the irises on one occasion, in an area 1 mm. below the area from which they obtained pupillary constriction in the macaque. Warwick found cell degeneration in the ipsilateral Edinger-Westphal nucleus and even more marked cell degeneration in the anteromedian nucleus following ciliary ganglionectomy and oculomotor nerve division. The first purpose of this paper is to report the results of stereotaxically controlled electrical stimulation of the nucleus for accommodation and adjacent areas.

The effects of accommodation on intraocular pressure were meticulously studied by Hess and Heine by electrical stimulation of the ciliary muscle and ciliary ganglion in several species, including the cat and monkey. They concluded that accommodation had no effect on intraocular pressure. Greaves and Perkins found no increase in intraocular pressure in the cat from stimulating the peripheral cut end of the oculomotor nerve if contractions of the extraocular muscles were eliminated with decamethonium iodide. However, Schmerl and Steinberg reported increased intraocular pressure in the rabbit while stimulating the apex of the orbit. Also, Armaly stimulated the ciliary ganglion in sympathectomized cats and recorded a significant decrease in intraocular pressure. The second purpose of this paper is to report the effects of accommodation and pupillary constriction, evoked by electrical stimulation of the parasympathetic component of the oculomotor nucleus, on intraocular pressure.

Materials and methods

Twelve female monkeys (Macaca mulatta), that weighed between 2.0 and 2.5 kilograms, were used in 15 experiments. Various anesthetic techniques were used: (1) intraperitoneal or intravenous pentobarbital in doses of from 60 to 125 mg., (2) halothane by inhalation, or (3) 30 to 50 mg. of intraperitoneal pentobarbital supplemented by 4 mg. of intramuscular Sernyl. The last technique was most satisfactory. In no discernible way did the anesthetic technique appear to alter the experimental results, but the most responsive animals were lightly anesthetized. Procaine 1 per cent was injected locally before the skin incisions were made.

All animals received endotracheal intubation and their heads were fixed in a stereotaxic apparatus. The head was shaved and a midline dorsal craniotomy was performed. Approximately 3 by 7 cm. of parietal bone was removed. The dura was incised and carefully retracted so that the superior sagittal sinus was not damaged. A No. 28 spinal needle, insulated to the tip with Insul-X served as a monopolar electrode. The indifferent electrode was a cylindrical platinum rod placed in the rectum.

The stereotaxic atlas devised for the macaque by Snider and Lee was used as a guide for all electrode placements. The electrode was inserted vertically from about 6 to 8 mm. anterior to the frontal interaural plane (coordinates A to A) and as close to the midline as practicable (coordinates B to L) and formed an angle of about 30 degrees with the midbrain axis. The electrode was moved downward in the midbrain in 0.5 mm. steps until the desired response was obtained (anywhere from coordinates H + 3 to H - 5), or the electrode was withdrawn and reinserted anterior or posterior to the first tract and the process repeated. Electrical stimuli were delivered by an AEL stimulator, Model No. 104A. The parameters used were 1 to 9 v., 100 per second frequency, and 1 msec. duration. Minimal stimuli were always employed to obtain the desired response. Stimuli were delivered in trains of up to 100 seconds.

Ocular, accommodative, and pupillary movements were observed and recorded cinematographically. The Purkinje images formed on the surface of the lens by an oblique light were observed and photographed. Retinoscopy (skiascopy)
with a slit retinoscope was performed when indicated by the standard ophthalmic technique. Intracocular pressure was recorded manometrically either in one eye or in both eyes simultaneously. A No. 25 gauge hypodermic needle was inserted into the anterior chamber at the limbus or at the center of the cornea and connected to a Statham pressure transducer, Model P23 DC. The baseline pressures were adjusted by raising or lowering a saline reservoir that was connected to the system through a three-way stopcock. Pressure changes were recorded by an ink-writing Grass oscillograph, Model 52-925-735. Systemic blood pressure was monitored from the femoral artery and intravenous drugs were injected by means of indwelling catheters in the femoral artery and vein. Heparin in small amounts was used to keep the polyethylene catheters patent.

In some experiments, to eliminate the influence of the extracocular muscles on intraocular pressure, curare (100 meg, per cubic centimeter) was given intravenously until respirations ceased. The animal then received artificial respiration. The amount of curare required was usually about 500 meg. Also, in some experiments, phenylephrine 10 per cent ophthalmic solution was instilled in the eye to produce mydriasis and facilitate the measurement of accommodation. Atropine 1 per cent and cyclopentolate 1 per cent were used as test drugs to produce paralysis of the ciliary muscle. The role of the extracocular muscles in producing changes in intraocular pressure was also studied by sequential cutting of their insertions from the globe during stimulation of the somatic efferent subnuclei of the oculomotor complex, and, on two occasions, the intracranial portion of the oculomotor nerve. In order to identify the stimulated points, electrolytic lesions were produced in the midbrain with coagulation currents. The animals were put to death painlessly and perfused by the intracardiac injection of refrigerated 10 per cent formalin. Standard histological techniques were used to localize the brain lesions.

Drugs used in these experiments were: halothane, Sernyl (Parke, Davis & Co.), sodium pentobarbital, procaine hydrochloride, d-tubocurarine chloride (Burroughs Wellcome & Co.), phenylephrine (Winthrop Laboratories), Cyclopentolate (Schieffelin & Co.), and atropine (Alcon Laboratories, Inc.).

Experimental results

The relationship between “iris-bulge” and accommodation of the eye. The response was evoked in ten experiments by electrical stimulation of the midbrain points and the intracranial segment of the oculomotor nerve. It was characterized by a conspicuous forward bulging of the pupillary or central portion of the iris which produced a marked convexity of the iris diaphragm and a marked decrease in the depth of the anterior chamber (Fig. 1). The extent of the bulging appeared directly proportional to the intensity of the stimulating voltage until a maximum response was obtained. On observation of the eye from the side during iris-bulge, the central portion of the lens appeared to become conical and to move forward into the anterior chamber. The following techniques were used to evaluate this phenomenon:

Retinoscopy (skiascopy). A dioptric change in the power of the lens was observed which was dependent on the

![Fig. 1. Photographs before and after electrical stimulation of the nucleus for accommodation in the oculomotor nuclear complex (see text). In A, the iris diaphragm is concave; in B, it is convex. The iris is pushed forward by the bulging of the anterior surface of the lens. Note that the diameter of the pupil is the same in both pictures.](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932995/ on 10/29/2018)
strength of the stimulus. At high voltages (5 to 9 v.) increases in refractive power of up to 10 diopters were measured. Increases of more than 10 diopters were probable in our young macaques. These increases could not be measured accurately by retinoscopy because the retinoscopic reflex was obscured by the miosis and ocular movements which resulted from current spread to adjacent areas when high voltages were used. When changes of less than 3 to 4 diopters were measured, little or no iris-bulge was observed.

Cinematography of the Purkinje images. Phenylephrine 10 per cent was instilled into the eye in which the iris-bulge was produced by stimulation of midbrain sites. After 30 minutes the pupil became widely dilated (diameter about 7 mm.) and the midbrain sites were restimulated. The movements of the Purkinje images reflected from the anterior and posterior lens surfaces were observed and photographed. During stimulation the anterior Purkinje image became smaller and moved forward and farther away from the posterior Purkinje image. Movements of the anterior lens surface appeared relatively unaffected by phenylephrine, while pupillary constriction was markedly diminished.

The effect of atropine and cyclopentolate instilled into the eye on the iris-bulge and accommodation evoked by electrical stimulation. These drugs completely blocked the response within 40 minutes after instillation.

The stereotaxic localization of midbrain sites that produce iris-bulge and changes in the retinoscopic reflex (accommodation). Iris-bulge was obtained in 12 experiments by stereotaxically controlled monopolar stimulation of midbrain sites that were attained during 19 different electrode insertions. The sites responsible for accommodation were localized to the anterodorsal region of the oculomotor nuclear complex in the so-called anteromedian nucleus (Fig. 2). This area extended about 2 to 3 mm. in a rostrocaudal direction and about 1 mm. to either side of the midline (coordinates A to A and R to L). Isolated iris-bulge and iris-bulge with pupillary constriction were evoked more frequently than isolated pupillary constriction.

The patterns of response from excitation of sites within the oculomotor nuclear complex. In two experiments the electrode was fortuitously inserted in the exact midline (Fig. 2). Low voltages (1 to 3 v.) evoked symmetrical iris-bulge (accommodation of more than 3 diopters) in both eyes without associated pupillary constriction or ocular movements as the electrode entered the rostral portion of the oculomotor nucleus. Gradually increasing the voltage (from 1 to 8 v.) produced the following superim-
posed phenomena in sequence: (1) bilateral symmetrical pupillary constriction, (2) bilateral symmetrical or asymmetrical downward ocular movement, (3) bilateral abrupt (phasic) adduction of the eyes, and (4) bilateral lid retraction. When the electrode was moved downward about 1 mm. from the site that produced isolated bilateral iris-bulge a site was reached in which low voltage stimulation produced both iris-bulge and pupillary constriction and 0.5 mm. below this site stimulation produced only bilateral pupillary constriction.

In ten experiments the stimulating electrode was angulated slightly off the midline because of technical problems or was deliberately inserted laterally about 1 mm. from the midline. The sequence of events, as the electrode was moved downward, was usually the same as in midline stimulation except that the responses were ipsilateral, i.e., isolated iris-bulge, iris-bulge and pupillary constriction, and isolated pupillary constriction. In some experiments iris-bulge and pupillary constriction could not be dissociated and each phenomenon occurred to a varying extent at all the sites of stimulation, but in most cases, iris-bulge was more intense than pupillary constriction in dorsal and rostral sites and the reverse was true from more ventral and caudal sites.

When the electrode was reinserted in different tracts at intervals of 1 mm. from left to right across the midline in a frontal plane (e.g., A₆, L₁; A₁, M(midline); A₄, R₁) the sequence of responses to stimulation was: (1) left ipsilateral iris-bulge or pupillary constriction or both, (2) bilateral iris-bulge or pupillary constriction or both, and (3) right ipsilateral iris-bulge or pupillary constriction or both. If the stimulus voltages were increased (e.g., 2 to 6 v.) at a lateral site which ordinarily produced ipsilateral reactions, responses were obtained in the contralateral eye. Also, these contralateral responses were of lower amplitude than the ipsilateral responses.

It was more usual to have ocular movements associated with iris-bulge and pupillary constriction than for these responses to occur as isolated phenomena. In rostral tracts, iris-bulge was associated with downward ocular movements that had an inward component and in more caudal tracts pupillary constriction was associated with ocular adduction.

The effect of stimulation of the parasympathetic nucleus on the intraocular pressure. As described above, stimulation produced accommodation or pupillary constriction or both, depending on the position of the electrode. Accommodative amplitudes of up to 10 diopters were obtained with intermittent stimulation at one per second and with prolonged stimulation. Even with such strong accommodative movements, associated with a marked decrease in the depth of the anterior chamber, no significant rise in intraocular tension was recorded (Fig. 4, upper trace). Maximal isolated pupillary constriction and pupillary constriction associated with accommodation also produced no change in intraocular pressure. Varying the baseline intraocular pressure from 0 to 50 mm. Hg had no effect on the absence of pressure response to accommodation or pupillary constriction. Prolonged stimulation of up to 100 seconds had no effect on intraocular pressure that could not be accounted for by extraocular muscle contraction or variations in blood pressure due to current spread into contiguous areas (Figs. 4, 5, and 6), as described below.

A common response from oculomotor nucleus stimulation was to obtain accommodation associated with increased extraocular muscle tone even when no ocular movements were visible. In these cases, there was a steep rise in intraocular pressure that appeared at first glance to be related to the accommodation. However, intravenous curare abolished these increases in intraocular pressure even when vigorous accommodative movements were still taking place.

During prolonged stimulation in or near the oculomotor nucleus, changes in sys-
temic blood pressure were observed which correlated in time with changes in intraocular pressure (Figs. 4 and 6). A common response was a slight decrease in systemic blood pressure and intraocular pressure upon cessation of the stimulus (Fig. 6). The reverse was also seen, namely, an increase in systemic blood pressure and intraocular pressure following cessation of the stimulus (Fig. 4, two lower traces).

In one experiment, intraocular pressure decay was studied during evoked accommodation with the opposite eye serving as control: the intraocular pressures in both eyes were elevated to 30 mm Hg and the gradual decrease in pressure in both eyes was observed. Accommodation evoked in one eye during this period of intraocular decay did not affect the slope of the decay curve of that eye as compared to the non-accommodating eye.

Discussion

Accommodation. The maximum accommodative range evoked in young macaques from the dorsorostral region of the oculomotor complex was from 10 to 12 diopters. This range of accommodation was previously found by Hess and Heine12 by stimulating the ciliary ganglion. A marked decrease in the depth of the anterior chamber accompanied high amplitudes of accommodation. The conical bulging movement of the central portion (collarette) of the iris, which accompanied these reactions, was a passive motion. It resulted from the contraction of the ciliary muscle which produced a forward movement of the anterior surface of the lens and an increase in the dioptric power of the eye. Conspicuous passive iris movement was easily seen with changes in dioptric power of the lens of at least 3 diopters. Accommodation of less than 3 diopters was observed only by retinoscopy.

Passive iris movements mainly, but also changes in the retinoscopic reflex and the Purkinje images, were used as indicators for stereotaxically mapping out the nucleus of accommodation. The concept of the morphology of the parasympathetic component of the oculomotor nucleus that we formulated from these experiments was as follows: The visceral efferent nucleus consists of two adjacent elongated cell masses that lie on both sides of the midline raphe in the anterior and dorsal part of the oculomotor nucleus. These cell masses extend from about 1 mm. to either side of the midline and about 3 mm. in a rostrocaudal direction. The innervation for the ciliary muscle and for the pupil appear to be entirely from the ipsilateral nucleus. There is a discrete cell mass that mediates accommodation alone, located dorsal and somewhat rostral to a discrete cell mass that mediates pupillary constriction alone. These cell masses are contiguous or there is an intermediate zone of admixture. The rostral part of the parasympathetic nucleus appears intimately associated with the somatic subnucleus for the inferior rectus muscle, and the caudal part with the subnucleus for the medial rectus muscle.

Our experiments support the idea that there is a discrete cell mass subserving accommodation and a discrete cell mass subserving pupillary constriction, but we believe them to be contiguous or overlapping in an intermediate zone. We concur completely with Warwick,4, 5 in that we believe the ocular parasympathetic nucleus to be a continuous cell mass and also that the innervations are ipsilateral. Warwick concluded from retrograde degeneration experiments that 93 per cent of cells in the ciliary ganglion innervated the ciliary muscle and 3 per cent the iris sphincter, a ratio of about 30 to 1 in favor of the ciliary muscle. This is reasonable since the ciliary muscle is many times larger than the iris sphincter. Our observations suggest that there are many more cells subserving accommodation than pupillary constriction since accommodation or accommodation with varying degrees of pupillary constriction was a much more frequently evoked response than isolated pupillary constriction.

Intraocular pressure. Accommodation
evoked by stimulation of the parasympathetic nucleus of the oculomotor complex did not cause a rise in intraocular pressure. This fact was confirmed for intermittent stimulation at one per second that produced maximum accommodation, in which the movements of the iris and lens seemed to resemble the vigorous action of a pump, as well as for prolonged stimulation for about 100 seconds (Fig. 4). Also, centrally evoked accommodation did not affect the intraocular pressure decay curve, and experimentally changing the baseline intraocular tension did not influence the results.

Stimulation of the somatic component of the oculomotor nucleus produced a steep rise in intraocular pressure due to compression of the globe, if there was simultaneous contraction of the extraocular muscles, especially the superior and inferior rectus muscles (Figs. 3, 5, and 6). Changes in systemic blood pressure were frequently associated with stimulation of the oculomotor complex. These vascular effects were probably due to spread of current into adjacent areas during prolonged stimulation and coincided with variations in intraocular pressure (Figs. 4 and 6). A frequent response was to have either a rise or a fall in blood pressure and intraocular pressure following stimulation (Fig. 4, second trace from the top, and Fig. 6).

From our experiments we conclude that the acts of accommodation and ciliary muscle contraction in the healthy macaque have no significant influence on intraocular pressure or on the regulation of aqueous humor dynamics. The advantages in our experimental approach were that we used an animal with a large accommodative amplitude (the cat has only about 3 diopter accommodative amplitude) and produced accommodation preganglionically by stimulating the central nucleus without disturbing the orbital contents at all.

Fig. 3. Traces showing the marked increase in intraocular pressure that resulted from electrical stimulation of the somatic oculomotor subnuclei. The increased pressure was caused mainly by the simultaneous contraction of the superior and inferior recti as shown in the lowest trace, since cutting the insertion of the superior rectus prevented most of the rise in intraocular pressure. IOP, Intraocular pressure; BP, blood pressure; STIM, stimulus; SR, superior rectus; MR, medial rectus.
Changes in the intraocular pressure from stimulation in or near the oculomotor nucleus were associated with simultaneous contraction of the extraocular muscles that produced compression of the globe. In addition, intraocular pressure changes were associated with changes in the systemic blood pressure. In our experiments these two factors were artifacts. However, it is possible that one or both are important.
means by which aqueous humor dynamics are influenced by the central nervous system. We obtained rises in intraocular pressure produced by tonic extraocular muscle contraction, that were unassociated with visible ocular movements. Also, as Von Sallmann and Lowenstein point out, focal vascular changes confined to the intraocular circulation may result from brain stimulation, since they found areas in the diencephalon which, when stimulated, produced variations in intraocular pressure that were unassociated with variations in systemic blood pressure or extraocular muscle activity. It is obvious that there is much more to be learned about the relationships between the intraocular pressure and the central nervous system.

In contrast to our results, Armaly obtained a decrease in intraocular pressure in sympathectomized cats from stimulating the ciliary ganglion. Further work will be needed to reconcile our work with his findings. Perhaps there are neuronal pathways that reach the ciliary ganglion from brain areas other than the oculomotor nucleus?

In our own thinking on this complex
matter we are not surprised at the fact that accommodation and the structural changes reported in the chamber angle accompanying accommodation\textsuperscript{14, 15} do not influence intraocular pressure. The eye appears to maintain its pressure equilibrium in spite of rather gross dynamic ciliary muscle contractions. Imagine the pommeling sensitive tissues might be subjected to if this were not the case!

**Summary**

1. Conspicuous bulging forward of the iris was evoked in the macaque by stereotaxically controlled electrical stimulation in the dorsal and rostral part of the oculomotor nucleus in the so-called anteromedian nucleus. The iris-bulge was a passive motion due to a conical forward bulging of the anterior lens surface which resulted in an increased dioptric power of the eye and a marked narrowing of the anterior chamber. Iris-bulge was observed when the eye was accommodating more than three diopters. Iris-bulge and retinoscopy were used as indicators that the nucleus for accommodation was being electrically stimulated in the midbrain.

2. As mapped by the responses in our experiments, the parasympathetic component of the oculomotor nucleus appears to be composed of paired elongated cell masses in the dorso-rostal portion of the oculomotor nucleus that lie close to the midline. Discrete innervation of the ipsilateral ciliary muscle arises from cells that are located dorsally and somewhat rostrally to the cells that innervate the ipsilateral iris sphincter. The cells that innervate these discrete functions are either contiguous, mixed, or overlap in an intermediate zone. The majority of the cells appear concerned with accommodation and a minority with pupillary constriction. Warwick's concept that the Edinger-Westphal nucleus and anteromedian nucleus form a continuous mass and are integral parts of the parasympathetic oculomotor nucleus is supported by these experiments.

3. Stimulation of the somatic oculomotor subnuclei produced a marked increase in the intraocular pressure which was due to compression of the globe by the simultaneous contraction of normally antagonistic muscles, especially the superior rectus and the inferior rectus. The increase in intraocular tension was eliminated by severing the extraocular muscles from the globe or by the intravenous injection of curare.

4. Stimulation of the parasympathetic nucleus that evoked accommodation or pupillary constriction or both, produced no change in intraocular pressure or change in the rate of outflow of aqueous humor. This observation was true regardless of the baseline intraocular tension and for prolonged stimulation up to 100 seconds as well as for maximum accommodative movements occurring at a frequency as fast as one per second.

5. Stimulation in or near the oculomotor complex frequently caused variations in systemic blood pressure, which coincided with small variations in intraocular pressure.

**REFERENCES**

8. Szentágothai, J.: Anatomical aspects of inhibitory pathways and synapses, in Florey,