The parasympathetic pathways to internal eye muscles

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The sphincter iridae and ciliary muscles of the alert monkey differ in their frequency response to intracranial electrical stimulation of the third nerve. Unilateral pupil constriction falls off when stimulation frequencies exceed 100 Hz., but brisk accommodation responses are obtained up to at least 1,000 Hz. Electrical stimulation of the short ciliary nerves in the anesthetized monkey produces good responses in both sphincter iridae and ciliary muscles to frequencies of at least 1,000 Hz. Local application of nicotine to the ciliary ganglion abolishes pupil constriction, but not accommodation, on electrical stimulation of the third cranial nerve proximal to the ciliary ganglion. It is concluded that the motor pathway for accommodation does not have a synapse in the ciliary ganglion while that for pupil constriction does.

In mammalian neurophysiology, the distinction between the voluntary control of skeletal muscle and the autonomic (i.e., involuntary) function of smooth muscle is so fundamental that many writers have remarked on the singularity of ocular accommodation, which is a voluntary function, being subserved by a smooth muscle. A

Bernheimer, however, stoutly maintained that exenteration of the eyeball causes retrograde degeneration in the third nerve nucleus, a finding which would suggest that some fibers go directly from midbrain motor regions into the eyeball without synapse. Bernheimer's view was opposed by Marina, but even the latter admitted there were some chromatolytic cells in or near the third nerve nucleus complex after exenteration of the eyeball in several species, including the monkey.

Warwick claimed that iridectomy leads to degeneration of only 3 per cent of the cells in the ciliary ganglion, while total exenteration of the bulb produces virtually total degeneration in the ciliary ganglion. He found no degeneration in the third nerve nucleus following either procedure.

In an experimental study in the monkey, Jampel and Mindel determined that sti-
ulation of various portions of the third nerve nucleus causes unilateral accommodation or pupil constriction and that the two functions could be elicited from regions which partially overlapped.

Against this background we offer the following experimental findings which mark an important distinction between the innervation of the ciliary muscle and that of the sphincter pupillae.

Method

Experiments of two kinds were conducted on young adult male monkeys, either Macaca speciosa or Cercopithecus atheiops.

In the first set of experiments, 0.9 per cent NaCl-filled micropipettes with an impedance of 1 to 3 MΩ were stereotaxically directed through a trephine hole in the skull to stimulate midbrain structures. The monkey had an implanted headgear which immobilized his head; otherwise, he was at liberty to move. In these particular experiments the monkey was unanesthetized and unmedicated. Stimulation was by trains of 0.5 msec. pulses at controlled frequencies and voltage; the current never exceeded 150 μamps, was usually 50 μamps, and occasionally was as low as 10 μamps. The monkey's accommodative state was determined by retinoscopy. Using a streak retinoscope it is easy to determine whether accommodation responses are binocular or unilateral. Since a monkey's interpupillary distance is 25 mm., the streak may be placed horizontally to cover both pupils and the reflex may be seen simultaneously in both eyes; when only one eye accommodates, a very striking "see-saw" effect is seen. Pupil constriction was monitored by inspection.

The second set of experiments was performed on the same monkeys at a later stage in their laboratory careers. They had experienced various neurologic interventions in the interim, but none had any demonstrable defect in the peripheral pathways to the eye. Under deep nembutal anesthesia the ciliary ganglion was approached via an extensive frontotemporal opening in the skull, removal of the frontal lobe, and excision of the roof and lateral wall of the orbit. The levator palpebrae, the superior and lateral recti, and a slit of the retractor bulbi were detached from the globe and retracted. Sufficient orbital fat was removed to expose the ciliary ganglion with its various roots. (In the monkey, the ciliary ganglion is intimately connected to the third nerve branch from the inferior oblique muscle, and does not exhibit a distinct motor root.) Bipolar electrodes were used to stimulate either the short ciliary nerves or the third nerve proximal to its connec-

tion to the ciliary ganglion. Accommodation was evaluated by retinoscopy and pupil constriction by inspection.

After preganglionic and postganglionic pupillary and accommodation responses to stimulation were recorded, a few drops of 10 per cent nicotine sulfate were applied to the ganglion and the responses to preganglionic and postganglionic stimulation again recorded. Now, stimuli were trains of 0.5 msec. pulses at 3 to 8 volts, at controlled frequency. The bipolar electrodes had in situ resistance in the 5 to 10 KΩ range.

On completion of the experimental procedures, the monkeys were killed by injections of nembutal and perfused with 10 per cent formalin. The ciliary ganglia on the side opposite that used for the experiment were dissected out and stained by overnight immersion in 2 per cent osmic acid. The stained ganglia were embedded in paraffin. Serial sections at 15μ were mounted, cleared, and covered, then examined for fibers passing through the ganglion without synapse.

Results

Stimulation of the mesencephalon in the alert monkey. It is possible, consistently, to induce binocular accommodation by trains of stimuli delivered to a midline region just dorsal and rostral to the third nerve nucleus, but this is by no means the only site yielding accommodation responses. Frequencies of 400 to 500 Hz. are most effective and frequencies below 200 Hz. progressively less so. In the site mentioned, stimulation results in the full near triad, with symmetrical convergence and pupil constriction accompanying accommodation. Depending on exact electrode placement, there may also be a concomitant infraversion or, rarely, supraversion with lid retraction. This full near triad response should be contrasted with the response seen when one stimulates among the third nerve roots after they have left the third nerve nucleus. Here stimulation causes unilateral accommodation when a frequency of 400 to 500 Hz. is used; oculomotor responses are seen but there is little accompanying pupil constriction. If the frequency of the stimulus train is lowered, the picture changes radically. Brisk pupil constriction confined to the ipsilateral eye occurs in a frequency range of 60 to 150 Hz.;
at frequencies above 250 Hz, only a transient flick of pupil constriction is seen, usually followed by slight pupil dilatation. At the frequencies where the pupil responds best to stimulation in the third nerve roots, accommodation response is sluggish. As stimulating frequency increases, accommodation responds more briskly and continues to do so up to 1,000 Hz. The differing frequency optima for accommodation and pupil constriction are shown in Fig. 1.

Does the large difference between the frequency optima for stimulating accommodation and pupil constriction imply a difference in physiology of the ciliary and sphincter iridae muscles, or is it rather a result of different neural pathways to the eye? To decide this, the ciliary ganglion and its roots were stimulated directly in anesthetized monkeys.

**Intraorbital stimulation.** Stimulation of the short posterior ciliary nerves causes both pupil constriction and accommodation. In contrast to the finding when stimulating the third nerve roots intracranially, both the sphincter and the ciliary muscle show good contractions throughout the frequency range up to 1,000 Hz. Thus, the poor response of the sphincter muscle seen when the third nerve roots are stimulated at frequencies above 150 Hz is not a consequence of the inability of the sphincter muscle to follow high frequency stimuli and may be the result of synapse in the ciliary ganglion. Previous work on cervical sympathetic ganglia in the rabbit has shown that autonomic ganglia begin to fail in the transmission of stimuli when rates of 100 Hz are approached. To prove that it is indeed the synapse in the ciliary ganglion that limits the frequency response of pupil constriction, the ciliary ganglion was painted with nicotine as described by Langley and Anderson. We find that stimulation of preganglionic fibers to the ciliary ganglion causes pupil constriction up to a frequency of 150 Hz before the application of nicotine, but stimulation is ineffective at any frequency after application of nicotine.

Accommodation responses to intraorbital stimulation of the third nerve, although perceptibly diminished, are still clearly seen after application of nicotine to the ciliary ganglion.

Thus the pathway for accommodation, as distinct from that for pupil constriction, either does not synapse (at least entirely) in the ciliary ganglion or if it does synapse entirely, the synaptic transmission is of
radically different character than in the pupil constrictor pathway.

**Anatomic study of the ciliary ganglion.** In serial sections of the ciliary ganglion, large numbers of myelinated fibers are seen to course together from the third nerve through the ganglion to the short ciliary nerves, but the tortuous path of fibers precludes tracing them individually from entry to exit. In lightly stained specimens the bundle is sufficiently prominent to be seen running across the surface of the ganglion.

**Discussion**

We cannot as yet determine with definitive precision what central structures we are stimulating to produce accommodation and pupil effects and thus cannot take a position concerning the exact localization of accommodation, pupil, and convergence functions in the various nuclear groups. The simultaneous release of the complete near triad by low threshold (10 µamps) electrical stimulation makes it likely that a center for the near triad exists in the midline near the rostro-dorsal border of the third nerve nucleus. From it, a presynaptic input probably goes to different groups of cells on each side of the midline, cells whose axons provide innervation, respectively, to the ipsilateral medial rectus, to the ciliary muscle, and to the sphincter pupillae (the last via a synapse in the ciliary ganglion). The observation that there is relaxation of the lateral rectus during convergence demands, in addition, an inhibitory pathway to the lateral recti (Fig. 2). Whether additional integrative paths to the eight vertical and oblique external eye muscles should be added to the schema is as yet an open matter. We have found a participation of these muscles in other purely horizontal conjugate movements and it seems likely that convergence above or below the horizontal plane would require some involvement of vertically acting muscles.

Although our demonstration of an uninterrupted motoneuron path to the ciliary muscle comes after acceptance of the opposite view for nearly a century, it requires surprisingly little reconciliation with conflicting evidence in the literature. Most studies on the ciliary ganglion have lumped accommodation and pupil constriction together. Usually only pupil constriction was
measured and its pathway contrasted with sympathetic and sensory pathways. Once the presence of a synapse in the ciliary ganglion was established, the clear findings of Bernheimer and Marina that there is central neuronal degeneration following exenteration of the eyeball came into disrepute. Lack of a synapse for the fibers to the ciliary muscle would at once reconcile these views: retrograde central degeneration after exenterio bulbi is due to the interruption of the nonsynapsing fibers for accommodation.

Warwick’s brief statement that he was unable to find central degeneration after exenteration conflicts with findings of several previous workers who had observed such degeneration even in the monkey. Warwick also saw almost complete cell lysis in the ciliary ganglion after complete exenteration, while 97 per cent of the cells in the ciliary ganglion were spared after iridectomy. He interpreted this as meaning that 97 per cent of the ciliary ganglion cells relate to the ciliary muscle and 3 per cent to the sphincter iridae. But it may also mean simply that iridectomy as carried out in his laboratory does not produce retrograde degeneration. Because the extent of chromatolysis is proportional to the amount of axon lost to the cell, it may be that an iridectomy that disturbed only the terminal ramifications of nerve fibers to the iris would result in little or no retrograde changes.

On the other hand, our results do not exclude the possibility that some nerve fibers reach the ciliary muscle after synapse in the ciliary ganglion. Yet the fibers that do not synapse can produce maximum accommodation by themselves; 440 Hz. stimulation in the central end of the third nerve, a stimulus that is not transmitted by the ciliary ganglion, causes full accommodation responses.

Fig. 2 incorporates the best current outline of the motor pathways to the internal eye muscles. The major difference in the efferent pathway for accommodation and pupil provides a welcome substrate for the fact that the former is prominently a voluntary function while the latter is not.

REFERENCES