

# Accommodation and Pupilloconstriction Areas in the Cat Midbrain

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**Abstract:** The results of our previous studies suggest that the rostral superior colliculus (SC) is involved in the control of accommodation in the cat. The accommodation-related area in the rostral SC projects into the pretectum and the mesencephalic reticular formation (MRF), indicating that these areas may also be involved in the control of accommodation. In this study, we tried to identify cat midbrain areas of accommodation and pupilloconstriction control by systematically mapping microstimulation responses. Three regions were found to evoke the accommodation response: the posterolateral pretectum, including the nucleus of the optic tract and the posterior pretectal nucleus; the posteromedial pretectum, including the nucleus of the posterior commissure (NPC) and adjacent commissural fibers; and the MRF area dorsolateral to the oculomotor nucleus. Pupilloconstriction was evoked by microstimulation of the posteromedial pretectum around the NPC and the anterior pretectum around the olivary pretectal nucleus. **Jpn J Ophthalmol 1997;41:43-48** © 1997 Japanese Ophthalmological Society

**Key Words:** Accommodation, mesencephalic reticular formation, pretectum, pupilloconstriction, superior colliculus.

## Introduction

Previous studies have suggested that the lateral suprasylvian (LS) area, the cortical area surrounding the middle suprasylvian sulcus (MSS) of the cat, is related to the control of lens accommodation.<sup>1-3</sup> The LS receives visual stimuli; some neurons respond to changes in ocular disparity and target size, and to motion in depth, which are major cues for accommodation.<sup>4-6</sup> Some LS neurons also exhibit burst discharges preceding the onset of spontaneous accommodation,<sup>2</sup> suggesting a significant effect on accommodation control.

Microstimulation of the LS evoked similar accommodative responses.<sup>1,3</sup> Systematic microstimulation of the cat LS identified the main site for evoking re-

sponses to low-threshold stimuli as the lower medial banks of the caudal MSS.<sup>3</sup> The LS also projects into other cortical areas, the thalamus, the pulvinar, the striatum, the pretectum, the superior colliculus (SC), and the pontine nuclei.<sup>7-10</sup> Bando et al<sup>2</sup> reported that approximately 70% of accommodation-related neurons were antidromically activated by stimulation of electrodes implanted in the pretectum and/or the SC, with average latencies of 2.4-2.5 milliseconds.

Injection of WGA-HRP into the low-threshold area of the cat LS produced dense labeling of axon terminals in the rostral portion of the ipsilateral SC, representing the central visual field.<sup>11</sup> Low-current (< 20  $\mu$ A) stimulation of the rostral SC corresponding to the terminal portion from the cortical accommodation area also produced accommodative responses.<sup>12</sup> These findings suggest that the rostral SC is important in brain-stem control of accommodation. The rostral SC projects mainly into the pretectum and the mesencephalic reticular formation (MRF),<sup>13</sup> possibly involving these areas in the control of accommodation.<sup>14</sup>

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In this study, accommodative and pupillary responses to microstimulation in the cat midbrain were recorded with a high-speed infrared optometer and pupillometer and systematically mapped in order to identify the areas related to control of accommodation and pupilloconstriction.

## Materials and Methods

### Animals

Fourteen cats weighing 2.5–3.5 kg were used in our experiments; all experimental protocols were approved by the Sapporo Medical University Animal Care and Use Committee and complied with the National Institutes of Health guidelines for animal care and use. Procedures for microstimulation and recording of accommodative responses in the cat have been described previously.<sup>12</sup> Each cat was deeply anesthetized with 2–4% halothane. After the trachea and the femoral vein were cannulated, anesthesia was discontinued and ketamine hydrochloride (initial dose: 25 mg/kg intramuscularly [IM]) and  $\alpha$ -chloralose (25 mg/kg intravenously [IV]) were administered. For accurate measurement of the dioptric changes, each animal was immobilized with pancuronium bromide (initial dose: 0.1 mg/kg IV, followed by 0.05 mg/kg IV every 40 minutes) and artificially ventilated. With the animal's head placed in a stereotaxic frame, a small parietal craniotomy was made for implantation of microelectrodes into the midbrain. Rectal temperature was maintained at 38°C by a feedback-controlled heating pad. During the experiment, supplemental doses of ketamine hydrochloride (15 mg/kg IM) and  $\alpha$ -chloralose (10 mg/kg IV) were administered every 30 minutes; heart rate and blood pressure were monitored to confirm the depth of anesthesia. For accurate measurement of accommodation, one pupil was dilated with 5% L-phenylephrine hydrochloride, which does not measurably affect the accommodative response;<sup>15</sup> the contralateral eye was used for measurement of pupil size.

### Procedures

Accommodative responses were continuously recorded with an infrared optometer (AR-1100, Nidek, Gamagouri, Japan) having a resolution of 0.01 diopter (D), basically analogous to the system developed by Cornsweet and Crane.<sup>16</sup> The ocular alignment of the experimental eye was continuously monitored by an infrared TV monitor mounted in the optometer. We have previously reported that responses detected by this system were abolished by

instillation of 1% atropine, indicating that these responses represent dioptric lens changes.<sup>12</sup> Pupil size was continuously monitored by an infrared pupillometer, which projects light from two infrared diodes (TLN110, Toshiba, Fuchu, Japan) onto the eye, and an infrared photodiode (TPS703, Toshiba, Fuchu, Japan), which detects the reflected light. The output of the photodiode was amplified by a conventional amplifier; system resolution was 0.2 mm<sup>2</sup>.

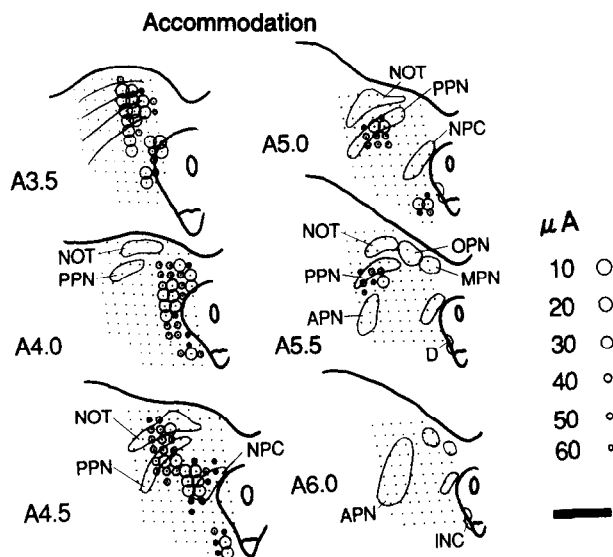
Tungsten microelectrodes insulated with Isonel 31 (Nisshoku, Osaka, Japan) were used for stimulation with a negative pulse of 0.2 milliseconds duration at 100–500 pulses/s for 0.5–3.0 seconds. We first located the low-threshold accommodation area in the SC that we had identified in our earlier study.<sup>12</sup> The midbrain area rostral to the low-threshold SC was then stimulated with approximately 60–100 electrode penetrations (0.5 mm intervals) for systematic mapping of each cat midbrain. Maximum current (60  $\mu$ A) was used first; if this produced no accommodative or pupilloconstrictive response, the electrode was advanced 500  $\mu$ m. When responses were produced, stimulus intensity was lowered to threshold level, defined as that which elicited 7–8 accommodative responses of > 0.03 D or pupilloconstriction of > 0.3 mm<sup>2</sup> for every 10 stimulations.

### Data Analysis

Accommodative and pupillary responses and trigger pulses for stimulation were recorded on magnetic tape, with a PCM data recorder (TEAC, Tokyo, Japan), for subsequent computer analysis. Data were digitized by computer at a sampling rate of 200 Hz; latency, amplitude, and duration of accommodative responses were analyzed by computer. We defined the onset of accommodative response as the moment when accommodative velocity reached 0.1 D/seconds. When the experiment was concluded, an electrolytic lesion (60  $\mu$ A for 5 sec) was made at the lowest threshold site in each cat. The animal was placed under deep barbiturate anesthesia and transcardially perfused with 10% formalin. The brain was removed and blocked in a stereotaxic plane; serial coronal sections (80  $\mu$ m thick) were stained with cresyl violet. A three-dimensional image of electrode tracks was made for each cat. Subdivisions of the pretectum were identified according to Berman,<sup>17</sup> and Avendano and Juretschke.<sup>18</sup>

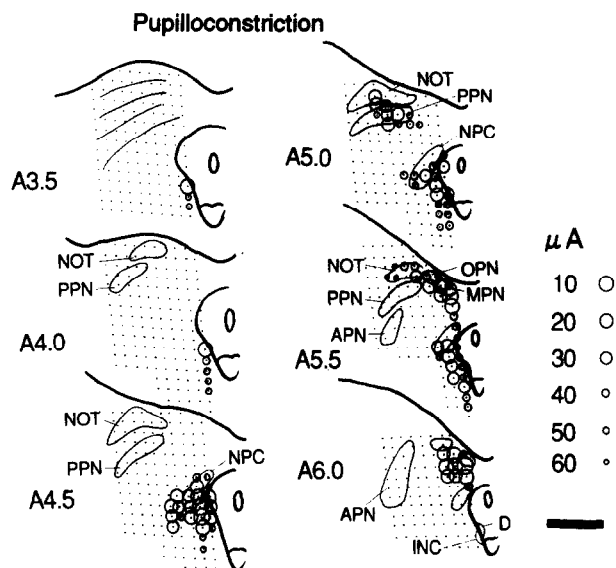
## Results

Negative pulses of 0.2 milliseconds at 250 Hz were used to systematically map the area from the rostral



**Figure 1.** Distribution of low-threshold sites (dots) of accommodation in midbrain coronal sections. Threshold at each site is indicated by diameter of circles shown on right. Dots without circles indicate sites ineffective at 60  $\mu$ A or less.

APN: anterior pretectal nucleus.  
D: nucleus of Darkschewitsch.  
INC: interstitial nucleus of Cajal.  
MPN: medial pretectal nucleus.  
NOT: nucleus of the optic tract.  
NPC: nucleus of the posterior commissure.  
OPN: olivary pretectal nucleus.  
PPN: posterior pretectal nucleus.  
Bar = 3 mm.



**Figure 2.** Distribution of low-threshold sites (dots) of pupilloconstriction in midbrain coronal sections. Threshold at each site is indicated by diameter of circles shown on right. Dots without circles indicate sites ineffective with stimulus currents of 60  $\mu$ A or less.

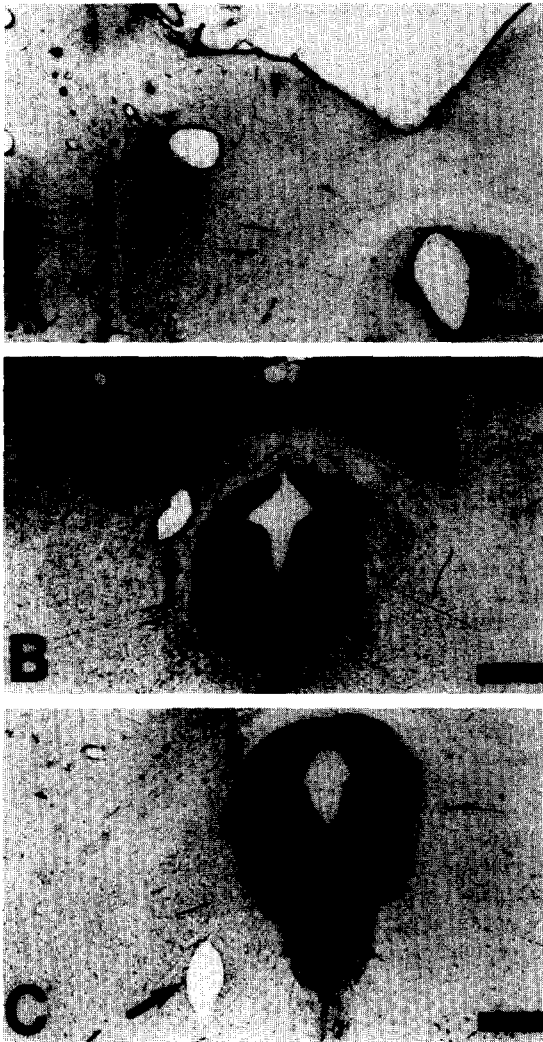
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SC to the rostral pretectum. Accommodative responses were seen in both eyes of the animal, but pupilloconstriction was dominant in the contralateral eye; therefore, accommodative responses and pupilloconstriction were recorded simultaneously in the ipsilateral and the contralateral eyes, respectively. Results were consistent in all 6 cat midbrains, which were completely mapped.

Figure 1 shows the distribution of low-threshold accommodation sites in serial coronal sections from the rostral SC to the rostral pretectum of one cat. Accommodative responses were stimulated in four regions: (1) the circumscribed area in the rostral SC corresponding to the site identified in our previous study;<sup>12</sup> (2) the posteromedial pretectum, corresponding to the nucleus of the posterior commissure (NPC); (3) the posterolateral pretectum, corresponding to the caudal optic tract nucleus (NOT) and the posterior pretectal nucleus (PPN); and (4) the mesencephalic reticular formation (MRF) region dorsolateral to the oculomotor nucleus. These areas

were well circumscribed and did not overlap if stimulus current was  $\leq 60 \mu$ A. There were no significant differences in the mean latencies of accommodative responses to stimulation of the posterolateral pretectum, the posteromedial pretectum, and the MRF, which were  $242.2 \pm 327$ ,  $230.7 \pm 26.9$ , and  $238 \pm 31.5$  milliseconds (mean  $\pm$  SD), respectively.

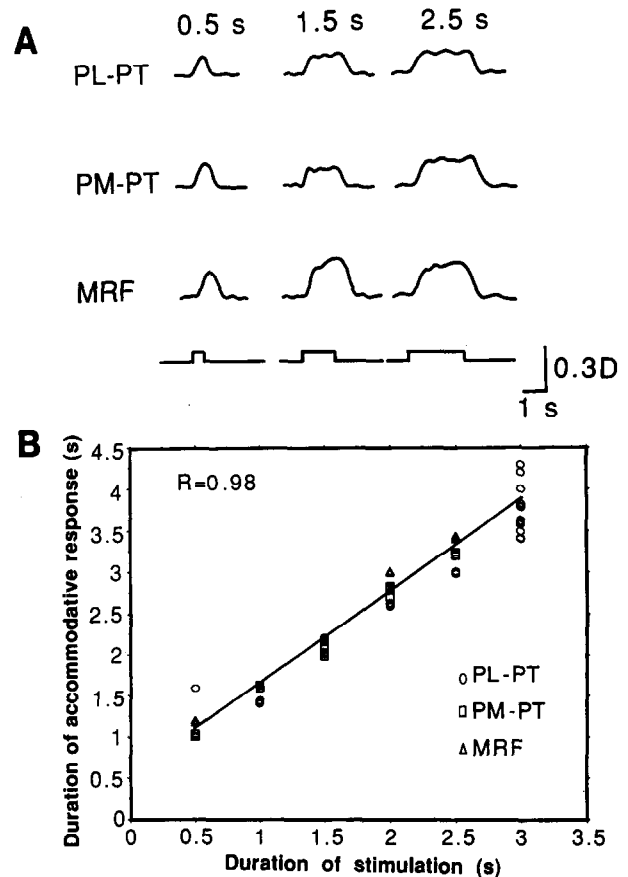
Figure 2 gives the distribution of low-threshold pupilloconstriction sites in serial sections of one cat, located mainly in two regions: (1) the anterior pretectum around the olivary pretectal nucleus (OPN), and (2) around and ventromedially to the NPC. Although the entire distribution pattern of pupilloconstriction sites deviated rostrally from the accommodation areas, both areas overlapped around the NPC and its ventromedial region. Both accommodation and pupilloconstriction were simultaneously produced in all cats by stimulation of the area around the NPC.



**Figure 3.** Photomicrographs showing electrolytic lesions (arrows) made at three low-threshold sites: (A) posterolateral pretegmentum; (B) posteromedial pretegmentum; (C) the MRF region dorsolateral to the oculomotor nucleus. Bars = 1 mm.

Figure 3 shows photomicrographs of coronal mid-brain sections indicating electrolytic lesions in the posterolateral pretegmentum, the posteromedial pretegmentum, and the MRF dorsolateral to the oculomotor nucleus, where weak current ( $< 20 \mu\text{A}$ ) produced accommodative responses. The lesions were located in the NOT at A4.5 stereotaxic coordinates, (Figure 3a); the NPC at 4.0 (Figure 3b); and the MRF at A4.5 (Figure 3c).

Figure 4 shows examples of accommodative responses from stimulation of each of three sites, and the relationships of the responses to stimulus duration (0.5–3.0 sec at each site). There was a high correlation between duration of response and duration of stimulation ( $r = 0.99$ ).



**Figure 4.** Accommodative responses evoked by stimulation of the three low-threshold sites, and change in the duration of response relative to duration of stimulation (A) Accommodative responses to microstimulation at the three low-threshold sites with stimulus durations from 0.5 to 3.0 sec. Positive deflections indicate increased diopter; lowest points indicate the on and off of stimulation. (B) Response duration and stimulus duration. MRF: mesencephalic reticular formation. PL-PT: posterolateral pretegmentum. PM-PT: posteromedial pretegmentum.

## Discussion

These findings suggest that, in addition to the rostral SC, three parts of the cat midbrain (the posterolateral pretegmentum, or NOT and PPN; the posteromedial pretegmentum, or the NPC and adjacent posterior commissural fibers; and the MRF dorsolateral to the oculomotor nucleus) are involved in the control of accommodation. Previous studies have shown that there is a dense projection of the LS cortical accommodation area into the rostral SC<sup>11,19</sup> and microstimulation of the rostral SC produced accommodative responses. The low-threshold area for evoking accommodation is in the superficial and intermediate layers of the rostral SC (Figure 1);<sup>12</sup> the accommoda-

tion-related area of the rostral SC projects into the pretectum and the MRF.<sup>13</sup> A previous anatomic study supports these results.<sup>20</sup> The low-threshold areas in the present study correspond closely to the areas that receive projections from the rostral SC.

Present results indicate that microstimulation of the posterolateral pretectum (NOT and PPN) can produce accommodation; no previous studies have indicated that cells in the NOT or PPN are related to the control of accommodation. Injections of muscimol (an inhibitory neurotransmitter agonist) into the posterolateral pretectum markedly inhibited responses to stimulation of the accommodation-related area of the rostral SC, suggesting that cells in this area are involved in the control of accommodation.<sup>13</sup> Microstimulation of the posterolateral pretectum did not produce pupilloconstriction, while pupilloconstriction is produced by stimulation of the OPN and the adjacent pretectal area (Figure 2). Previous studies have also reported that the pretectum, especially the OPN, is involved in the control of pupillary movement.<sup>21-24</sup>

In the present study, microstimulation of the NPC and the adjacent posterior commissural fibers produced both accommodation and pupilloconstriction. Hultborn et al<sup>23</sup> reported that iris bulging caused by accommodation was observed occasionally when these areas were stimulated. A previous study indicated that pupilloconstriction results from microstimulation of the NPC.<sup>25</sup> It appears that the NPC may be a neural substrate for mediating the interaction between accommodation and pupilloconstriction.

Microstimulation of the MRF region dorsolateral to the oculomotor nucleus produced both accommodation and pupilloconstriction. In alert monkeys trained to fixate on a target, MRF neurons discharged in association with accommodative responses, ocular vergence, or both.<sup>26,27</sup> Bando et al<sup>28</sup> also reported that neurons discharged before spontaneous accommodation were found in the cat MRF. These cells are confined to a small region dorsolateral to the oculomotor nucleus in both the cat and the monkey; therefore this region of the MRF, corresponding to the low-threshold MRF area in the present study, could be a neural substrate for mediating the interaction of accommodation and vergence. MRF involvement in the control of pupilloconstriction is, as yet, not clearly understood. Efferent fibers from the NPC pass through this region;<sup>16</sup> therefore it is possible that pupilloconstriction is produced by stimulation of these fibers, but not by stimulation of the MRF itself.

Efferent connections of the pretectum and the

MRF in the accommodation control system are unknown. Results of previous anatomic studies indicate that the pretectum projects into the oculomotor nucleus.<sup>16,29,30</sup> Zhang et al<sup>31</sup> reported that ocular near-response cells in the portion dorsomedial to the oculomotor nucleus could be antidromically activated from the oculomotor nucleus. This suggests that accommodation-related signals from the pretectum and the MRF are transmitted directly to the oculomotor nucleus. We therefore believe that the NOT, the PPN, and the MRF are related to the control of accommodation, and the OPN is related to pupilloconstriction. The NPC may be involved in control of both accommodation and pupilloconstriction.

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