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Role of intrinsic synaptic circuitry in collicular sensorimotor integration

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ABSTRACT **The superficial gray layer of the superior colliculus contains a map that represents the visual field, whereas the underlying intermediate gray layer contains a vector map of the saccades that shift the direction of gaze. These two maps are aligned so that a particular region of the visual field is represented directly above the neurons that orient the highest acuity area of the retina toward that region. Although it has been proposed that the transmission of information from the visuosensory to the motor map plays an important role in the generation of visually guided saccades, experiments have failed to demonstrate any functional linkage between the two layers. We examined synaptic transmission between these layers *in vitro* by stimulating the superficial layer while using whole-cell patch-clamp methods to measure the responses of intermediate layer neurons. Stimulation of superficial layer neurons evoked excitatory postsynaptic currents in premotor cells. This synaptic input was columnar in organization, indicating that the connections between the layers link corresponding regions of the visuosensory and motor maps. Excitatory postsynaptic currents were large enough to evoke action potentials and often occurred in clusters similar in duration to the bursts of action potentials that premotor cells use to command saccades. Our results indicate the presence of functional connections between the superficial and intermediate layers and show that such connections could play a significant role in the generation of visually guided saccades.**

The superior colliculus receives sensory information about the location of objects and then processes this information to initiate motor command signals for the saccadic head and eye movements that orient gaze toward objects of interest (1). The proximity of these functions within the same structure makes the superior colliculus a powerful model for studying the fundamental problem of how the brain integrates sensory and motor systems to produce behavior.

Neurons in the superficial gray layer of the superior colliculus receive input from the retina and visual cortex (2–9). These cells respond to visuosensory stimulation, and their receptive fields are arranged to form a retinotopic map of the visual field (10, 11). In contrast, cells in the intermediate gray layer receive input from the substantia nigra, cerebellum, frontal eye fields, and several sensory systems (12–16), and project primarily to the brainstem circuits that generate saccades (13, 17). Correspondingly, these neurons exhibit sensory responses or presaccadic command signals (1, 2, 18). The vectors of the saccades commanded by the premotor cells vary systematically with location in the intermediate layer to form a motor map that is in register with the visuosensory map in the overlying superficial layer (2, 3).

The spatial alignment of the sensory and motor maps could reflect a mechanism for transferring information from sensory cells that encode the presence of stimuli in a particular region of the visual field to premotor cells that direct gaze toward that region (3). However, this appealing idea has not yet been confirmed experimentally; even though anatomical studies suggest that the superficial layer cells project to the intermediate layer by both monosynaptic and polysynaptic pathways (13, 24–28), there is no physiological evidence that superficial cells contribute to the generation of command signals by the premotor neurons. Thus, alternative pathways have been proposed to account for the transfer of visual information to the intermediate layers (2, 15, 19–23).

In the present study, we examined the interactions between the visuosensory and premotor neurons by directly analyzing synaptic transmission between them. We performed the analyses *in vitro* by stimulating the superficial layer while using high-resolution, whole-cell patch-clamp methods to record the synaptic responses of the premotor cells. For these experiments, we used slices of the large and well differentiated superior colliculus of the tree shrew, *Tupaia belangeri*. The sharply defined borders between the layers in this animal facilitate definition of the anatomical and functional relationships of cell types (13, 24). Our experiments demonstrate a strong and highly organized synaptic linkage between these two neuronal populations and point toward an important role for these connections in visuomotor transformations.

METHODS

Slice Preparation. Collicular slices were obtained as described previously (13, 24). Tree shrews were anesthetized with sodium pentobarbital and perfused with a chilled oxygenated solution containing 246 mM sucrose, 2.5 mM KCl, 1 mM NaH_2PO_4, 1.3 mM $MgSO_4$, 26.2 mM $NaHCO_3$, 11 mM d-glucose, 2.5 mM $CaCl_2$, and 1.85 mM kynurenic acid. A block of tissue that included the superior colliculus was removed and sectioned into 200–400-μm coronal slices. The slices were collected into an oxygenated chamber where they rested on a membrane interface over the sucrose-saline solution at 35°C for 40 min. They then were transferred to a membrane over physiological saline (123 mM NaCl replacing the sucrose in the above solution) containing kynurenic acid and then equilibrated at room temperature for about 1 hr.

Patch-Clamp Recordings. Methods similar to those described in Edwards *et al.* (29) were used to make whole-cell patch-clamp recordings from individual collicular neurons. Patch pipettes (3–7 MΩ resistance) were filled with internal solution (118 mM K-gluconate 2 mM NaCl 20 mM Hepes 4 mM $MgCl_2(6H_2O)$ 4 mM $Na_2ATP(2.5H_2O)$ 0.4 mM Na-GTP 10 mM EGTA, pH 7.3–7.4, ≈285 mOsmolal) containing the

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Abbreviations: EPSC, excitatory postsynaptic current; SGI, stratum griseum intermedium or intermediate gray layer; SGS, stratum griseum superficiale or superficial gray layer.

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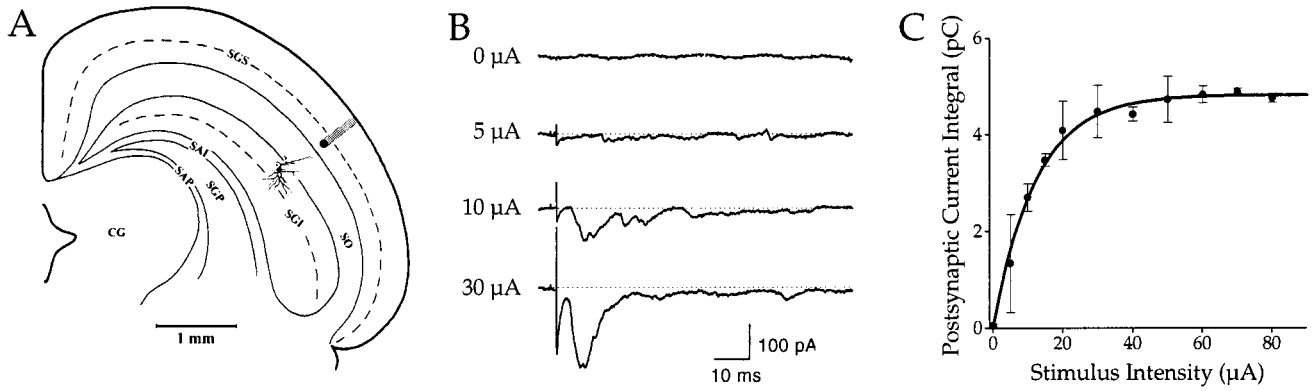

FIG. 1. Synaptic transmission between the superficial (SGS) and intermediate (SGI) layers. (*A*) Diagram of a collicular slice showing a biocytin-labeled cell in upper SGI located directly below the stimulating electrode track (gray rectangle and closed circle) in lower SGS. The subdivisions between upper and lower parts of these layers are indicated by dashed lines. (*B*) Postsynaptic currents evoked in the cell shown in *A* in response to stimuli of varying intensities. (*C*) Increasing stimulus intensity recruits additional synaptic inputs. Synaptic responses were measured in a cell different from the one shown in *A* and *B* and quantified by integrating the postsynaptic currents over time. Each point is an average of three responses. This cell was held at −85 mV. CG, central gray; SAP, stratum album profundum or deep white layer; SAI, stratum album intermedium or intermediate white layer; SGI, stratum griseum intermedium or intermediate gray layer; SGP, stratum griseum profundum or deep gray layer; SGS, stratum griseum superficiale or superficial gray layer; SO, stratum opticum or optic layer.

neuronal tracer biocytin at a concentration of 0.3–0.5%. Diffusion of this solution into the cytoplasm was used to label individual cells with the biocytin. After the experiments, the slices were fixed and either cut into 50-μm sections or processed without sectioning. The histological procedures to visualize biocytin were identical to those used in previous studies (13, 24).

Electrical stimuli were delivered to the slice through an array (1.2–2.4 mm width) of eight tungsten wire electrodes (NB Labs, Denison, TX) via a switching multiplexer and stimulus isolation unit. Stimuli consisted of current pulses 0.5 msec in duration that ranged from 1 to 100 μA. Postsynaptic currents evoked by these stimuli were recorded by a Warner PC501A amplifier, digitized by an Axon 1200 series Digidata A/D board, acquired and analyzed by pCLAMP, and plotted with Origin software (Microcal, Amherst, MA).

RESULTS

Our results are based on recordings from 39 neurons in collicular slices from 16 tree shrews. Of these neurons, 16 were successfully filled with biocytin for subsequent anatomical study. Because it is significantly less difficult to obtain whole-cell recordings in young animals (29), we restricted our attention to animals ranging from 8 to 28 days old. By 20 days, tree shrews are active and exhibit saccades. At all of these ages, we found strong synaptic transmission between the superficial and intermediate layers.

A single current pulse delivered to the lower superficial gray layer evoked synaptic responses in 30 of the 39 intermediate layer neurons. Twenty-six of these 30 cells were located in the upper part of the intermediate gray layer. Examples of the responses evoked in upper intermediate gray layer neurons are shown in Figs. 1–4, and Fig. 5 illustrates responses from a cell in the lower part of this layer.

In the cell illustrated in Fig. 1*A*, a single stimulus pulse delivered to the superficial gray layer evoked large inward postsynaptic currents (Fig. 1*B*). Such responses could be evoked by stimuli as small as 5 μA and occurred after latencies of several milliseconds. These features indicate that the responses result from activation of synaptic inputs near the stimulating electrode, rather than from direct current spread to the premotor cell dendrites in the optic layer. Because extrinsic pathways to the intermediate layer enter the superior colliculus through its deeper layers (12, 14), they are unlikely to have been activated by these small stimuli. Increasing stimulus strength yielded postsynaptic responses of larger amplitude and shorter latency (Fig. 1 *B* and *C*), indicating that the premotor cells receive synaptic input from multiple presynaptic neurons. These results are consistent with the suggestion that the two layers interact via monosynaptic and polysynaptic projections (24).

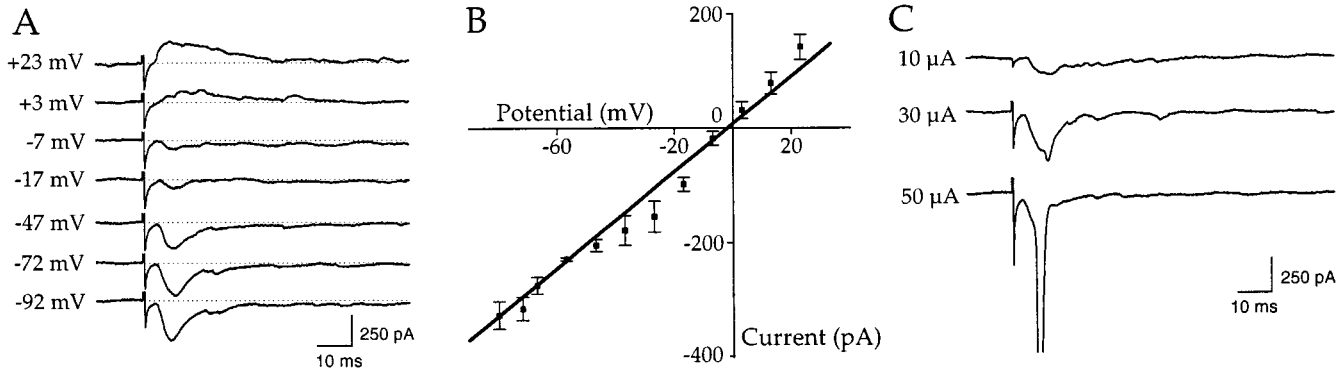

FIG. 2. Excitatory synaptic transmission between superficial and intermediate layer neurons. (*A*) Synaptic currents evoked while holding a premotor neuron at different membrane potentials. The currents increased with increasingly negative holding potentials and reversed their polarity at potentials near 0 mV. (*B*) Relationship between the peak amplitude of postsynaptic currents and the membrane potential. Each point represents the mean (± SEM) of four responses in the same cell. The reversal potential is approximately 0 mV. (*C*) Whereas small stimuli evoked small EPSCs, the largest stimuli were capable of evoking action potentials (off-scale on the lowest current trace).

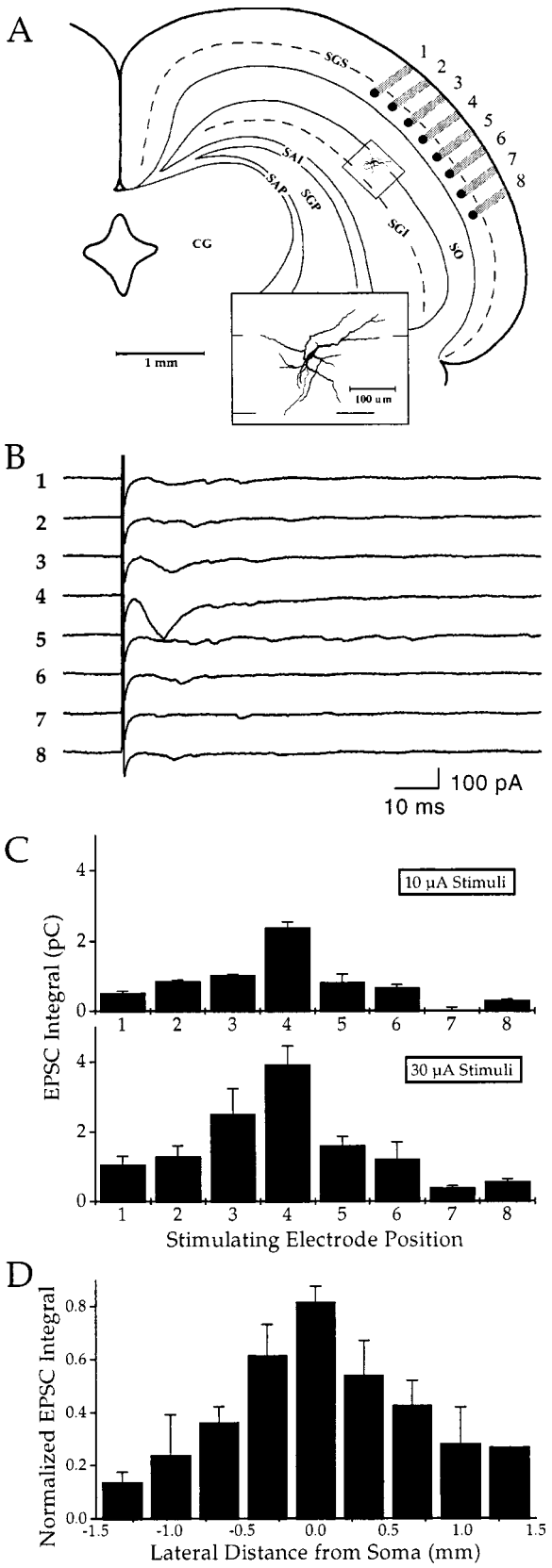

FIG. 3. Spatial tuning of the synaptic responses of premotor cells. (*A*) Location of a stimulating electrode array in SGS and the upper SGI cell from which the data in *B* and *C* were obtained. The cell was located below stimulating electrode 4. (*B*) EPSCs evoked by electrode 4 were larger than those evoked by other electrodes. (*C*) Relationship between postsynaptic responses and stimulating electrode position obtained from the cell shown in *A* at two different stimulus intensities. EPSCs were quantified by measuring their time integral, and the values shown represent the mean and standard error determined from responses to three stimuli. (*D*) Average spatial tuning characteristics of eight premotor neurons. The abscissa indicates the lateral distances between the cell somata and the long axis of the stimulating electrodes, and the ordinate indicates the mean and standard error of EPSC integrals, which were normalized to the largest responses measured for each cell. For definitions of abbreviations used in *A*, see the Fig. 1 legend.

Two lines of evidence indicated that these synaptic responses were excitatory postsynaptic currents (EPSCs). First, by varying the holding potential of the premotor cell, we could determine the reversal potential of the postsynaptic currents (Fig. 2*A*). Hyperpolarizing the cell to potentials more negative than the usual holding potential of −65 mV invariably caused the inward currents to become larger, whereas depolarizing the membrane potential caused them to become smaller. The currents reversed polarity at approximately 0 mV, becoming outward currents at positive membrane potentials (Fig. 2*B*). The mean value of this reversal potential was −1.7 ± 2.6 mV in four experiments. This reversal potential indicates an excitatory postsynaptic response, presumably caused by a relatively nonselective increase in postsynaptic cation permeability (30). Second, the largest EPSCs, up to 500 pA in amplitude, were capable of evoking action potentials even though the somatic membrane potential was voltage-clamped at potentials more negative than the threshold for action potentials (Fig. 2*C*). Although such results indicate the expected imperfect spatial control of postsynaptic membrane potential during large, regenerative current flow (31), they unambiguously identify the excitatory character of the postsynaptic response. Thus, sensory neurons in the superficial layer strongly excite premotor cells in the intermediate layer.

Previous anatomical analyses have suggested column-like connections between the layers of the superior colliculus (13, 24). To examine the spatial organization of the excitatory synapses innervating the premotor neurons, we used an array of electrodes to stimulate multiple locations within the lower superficial gray layer. In the experiment illustrated in Fig. 3*A*, the cell soma was located in the upper part of the intermediate gray layer and below electrode four of the array of eight electrodes. Stimuli applied consecutively to each of the electrodes evoked EPSCs that varied in amplitude depending on electrode position (Fig. 3*B*), with the largest currents evoked by electrode 4. Such spatially tuned responses were observed regardless of stimulus intensity, with the largest EPSCs always evoked by electrodes located in the region of the superficial gray layer directly dorsal to the cell (Fig. 3*C*). This tuning was a consistent feature of our recordings, as can be seen from the relationship between EPSCs measured in eight cells and the lateral distance between the stimulating electrode and the cell bodies (Fig. 3*D*).

A remarkable feature of synaptic transmission between the sensory and premotor neurons is that a single brief stimulus applied to the superficial layer usually evoked EPSCs with multiple peaks, often producing prolonged bursts of EPSCs that could outlast the stimulus by a factor of more than 100. Such bursts are evident in the EPSC recordings shown in Fig. 1*B* and are documented in two other cells illustrated in Fig. 4 *A* and *B*. Bursting behavior was observed in 20 of 30 cells from which EPSCs were recorded in response to superficial layer stimulation. It is possible that bursts were not observed in the remaining cells because of the loss of synapses during slicing. Bursts ranging from 10 msec to longer than 100 msec in duration were evoked by low-intensity stimuli, and sometimes had action potentials superimposed on them. The duration of the EPSC bursts was not a strict function of stimulus intensity in a given cell; despite the fact that higher intensity stimuli

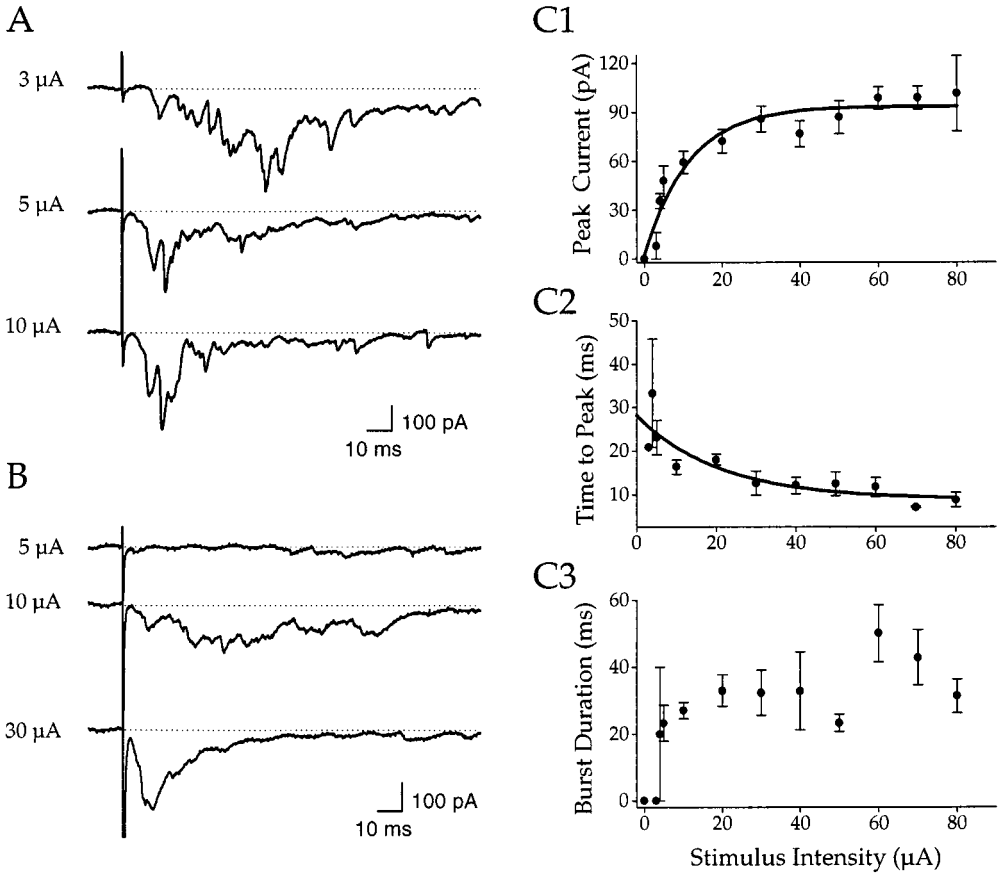

FIG. 4. (*A* and *B*) Clusters of EPSCs evoked by different stimulus intensities in two cells located in the upper intermediate gray layer. (*C*) Relationships between the intensity of single stimulus pulses and magnitude (*C1*), latency (*C2*), and duration (*C3*) of evoked bursts of EPSCs. Each point is based on three responses in a single neuron.

evoked larger (Fig. 4*C1*) and shorter latency (Fig. 4*C2*) responses, there was no detectable trend in burst duration (Fig. 4*C3*). This behavior is consistent with the bursts resulting from a regenerative process that must be initiated by a stimulus but is not immediately terminated by its cessation.

Although most of our measurements were made from neurons in the upper intermediate gray layer, we recorded synaptic responses from four cells located in the lower part of this layer. Previous anatomical results suggest that the projections from the superficial layer to the lower intermediate gray layer cells are polysynaptic and less direct than those to cells of the upper intermediate layer (24). Fig. 5*A* illustrates one cell that closely resembles the lower intermediate gray layer cells described previously (24). Such cells responded to stimulation of the superficial layer in ways qualitatively similar to the responses of the cells in the upper intermediate layer. For example, their bursts of synaptic responses were dispersed over periods of 100 msec or longer (Fig. 5*B*) and spatially tuned (Fig. 5*C*). In summary, stimulation of superficial layer neurons excites both upper and lower neurons within the intermediate layer, though there may be quantitative differences in their postsynaptic responses.

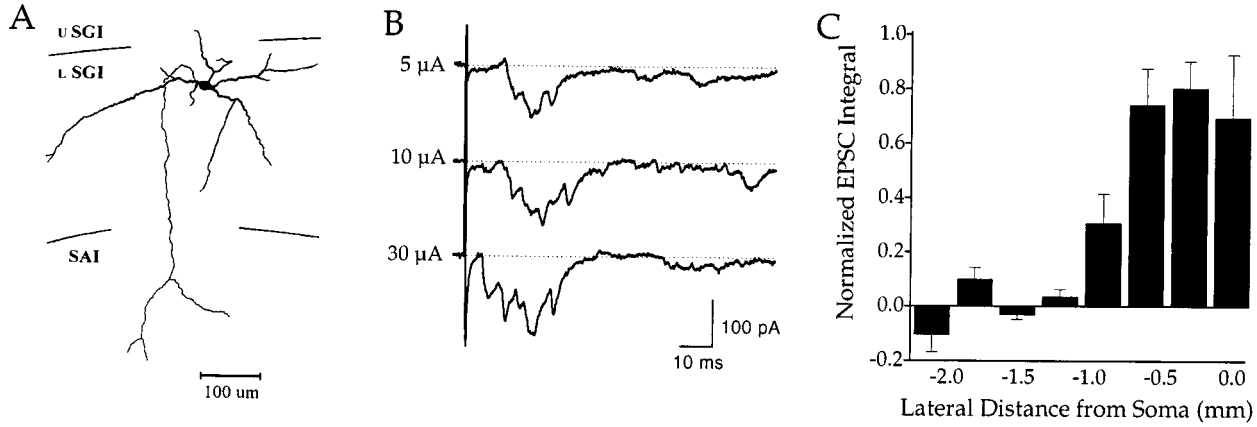

FIG. 5. Synaptic responses of a cell in the lower intermediate gray layer. (*A*) The axon of this neuron descends to exit the colliculus through its deeper layers. (*B*) Prolonged bursts of EPSCs evoked after single stimuli of different intensities. (*C*) Relationship between postsynaptic responses and stimulating electrode position. This cell was located below the last electrode in the array (i.e., 0.0 mm). For definitions of abbreviations used in *A*, see the Fig. 1 legend.

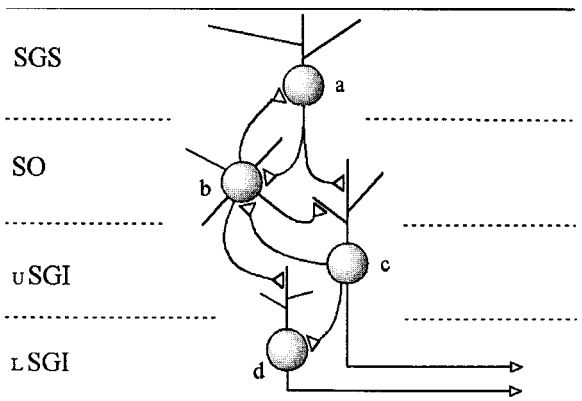

FIG. 6. Summary of collicular circuitry in the tree shrew (24). Cells in the lower SGS (a) project to the optic layer where they contact either optic layer cells (b) or apical dendrites of premotor cells in upper SGI (c). Optic layer cells project to the optic layer (SO) as well as to the adjacent layers. Premotor cells in lower SGI (d) receive input from either SO or upper SGI cells. L, lower; SGI, stratum griseum intermedium or intermediate gray layer; SGS, stratum griseum superficiale or superficial gray layer; SO, stratum opticum or optic layer; U, upper.

DISCUSSION

Many models have been proposed for the intrinsic circuitry of the superior colliculus. Although these models make specific predictions about the interactions among collicular cell types, most of these predictions have never been directly tested. In the present experiments, the use of patch-clamp methods has allowed us to measure synaptic transmission within the superior colliculus. The main significance of our work is the exploitation of the technical advantages of this approach to examine the functional relationships between cells in the visuosensory and premotor layers of the superior colliculus. Because of the difficulty in obtaining stable recordings in adult animals, the tree shrews used in these experiments were 1 month or less in age. However, we believe that our results are relevant to previous studies of saccades in adult animals because robust evoked responses were recorded from intermediate layer cells in the 1-month-old animals. Further, previous anatomical experiments indicate that the pathways between the superficial and intermediate layers persist in adult animals (13, 24).

We have obtained evidence for a functional link between the superficial and intermediate layers. Because of the low stimulus currents used and the latencies of the evoked responses, we presume that our stimuli were confined primarily to the superficial layer and activated superficial layer neurons, which then produced EPSCs in the premotor neurons via monosynaptic and polysynaptic pathways (ref. 24; Fig. 6). It is possible that some EPSCs in the premotor neurons could arise from antidromic activation of optic layer cells that occasionally project to both the superficial and intermediate layers (ref. 24; Fig. 6, cell b). However, because optic layer cells share the visuosensory properties of deep superficial layer cells (32), this alternative is also consistent with the view that intrinsic circuits link the visual and premotor layers.

Our experiments confirm anatomical evidence for connections between these layers (refs. 13 and 24–28; Fig. 6), and extend beyond the anatomy by revealing functional properties of these connections. These connections are largely excitatory, are spatially organized in a columnar fashion, and often produce bursts of EPSCs. These findings have several implications for the function of the circuitry linking the superficial and intermediate layers.

Spatial Organization of the Linkage Between the Superficial and Intermediate Layers. The results obtained by stimulating across the width of the superficial layer demonstrate that the excitatory influence of neurons in this layer on the intermediate layer cells is functionally columnar. These physiological data correlate well with previous anatomical analyses that revealed column-like connections between the layers of the tree shrew (13, 24). The axonal arbors of both the lower superficial gray and optic layer neurons as well as the dendritic fields of the cells in the intermediate layer are horizontally restricted; this arrangement could provide the structural substrate for the spatially tuned synaptic connections revealed by our electrical recordings.

The lower superficial layer receives projections from multiple cortical visual areas as well as from the retina (4, 24), suggesting that the intrinsic circuitry revealed by our experiments may transfer to presaccadic cells retinotopically organized information from many diverse visuosensory centers. In primates, cells in the lower superficial and optic layers give enhanced responses to stimuli that have been selected to become targets of saccades (32). Because these enhanced responses distinguish stimuli of special interest to the organism, the synaptic influences of these neurons on intermediate layer cells may contribute to the selection of the most salient target for a saccade from an array of stimuli. Additional pathways, such as one arising in the frontal eye fields (15, 16), project directly to the intermediate layer and also may contribute to the selection of saccades (15, 22, 33).

Contribution of the Descending Intracollicular Pathway to the Generation of Saccades. In most of the intermediate layer cells that we examined, a brief electrical pulse delivered to the lower superficial gray layer evoked prolonged bursts of EPSCs that were 100 msec or longer in duration. These bursts of EPSCs could be caused by prolonged trains of action potentials in the presynaptic superficial layer neurons or by the recurrent activity of intervening synaptic circuits. One possible substrate for the latter is the optic layer cells; some of these cells both receive projections from and project to superficial layer cells (ref. 24; Fig. 6, cell b) and might provide a positive feedback loop that enhances and sustains responses evoked by a brief stimulus to the superficial layer.

The characteristic electrical output of premotor neurons in the primate intermediate layer is presaccadic bursts of high-frequency action potentials (18, 19, 34). Because individual EPSCs were often capable of evoking action potentials in premotor cells, it is possible that the bursts of EPSCs could generate bursts of action potentials *in vivo*. Further evidence for this possibility is that the durations of the EPSC bursts evoked by superficial layer stimulation often were as long as the durations of the presaccadic bursts of action potentials (18, 19, 34). Although it has been reported that activity in the superficial layers is not sufficient to evoke a command signal for a saccade from the underlying premotor cells (22), it is possible that transmission between these layers is modulated by tonic inhibition from the substantia nigra or the rostral fixation zone of the superior colliculus (35–37), which were not present in our collicular slices. This possibility would require that the *in vivo* generation of a visually triggered burst of action potentials in these premotor cells depends on the coincidence of excitatory input from the superficial layer with a cessation of tonic inhibition (35, 36).

Our proposal that the superficial layer input to premotor cells is sufficiently powerful and long-lasting to evoke saccades is consistent with the argument that the "visual" responses of visuomotor cells are capable of initiating short latency express saccades (19, 38). Our data suggest further that the short latency of express saccades can be accounted for by pathways from the retina or visual cortex that contact premotor cells of the intermediate layer after a single relay within the lower superficial gray layer. The spatial selectivity of express saccades (39) is consistent both with the columnar excitation that links the superficial and intermediate layers and with the spatial selectivity of nigral disinhibition (35, 36). The partici-

pation of the pathway from the superficial to the intermediate layer in express saccades also is consistent with findings that lesions of either the superior colliculus or the geniculostriate system abolish express saccades (40). The latter lesions could abolish express saccades if the pathways from the visual cortex to the superficial gray layer (4, 5) mediate express saccades. Alternatively, the removal of these corticotectal pathways could disrupt the flow of information from the superficial to the intermediate layer that reaches the superior colliculus directly from the retina (41).

Whether or not these particular hypotheses are correct, our results provide compelling support for the view that intrinsic circuitry linking the superficial and intermediate layers is present and plays an important role in determining the motor output of the superior colliculus. Equally important, these data demonstrate the value of the *in vitro* patch-clamp method as a means to test hypotheses about the role of intrinsic collicular circuitry in sensorimotor integration.

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