Modification of Saccadic Eye Movements by GABA-Related Substances. I. Effect of Muscimol and Bicuculline in Monkey Superior Colliculus

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SUMMARY AND CONCLUSIONS

1. Our previous observations led to the hypothesis that cells in the substantia nigra pars reticulata (SNr) tonically inhibit saccade-related cells in the intermediate layers of the superior colliculus (SC). Before saccades to visual or remembered targets, cells in SNr briefly reduce that inhibition, allowing a burst of spikes of SC cells that, in turn, leads to the initiation of a saccadic eye movement. Since this inhibition is likely to be mediated by γ-aminobutyric acid (GABA), we tested this hypothesis by injecting a GABA agonist (muscimol) or a GABA antagonist (bicuculline) into the superior colliculus and measured the effects on saccadic eye movements made to visual or remembered targets.

2. An injection of muscimol selectively suppressed saccades to the movement field of the cells near the injection site. The affected area expanded over time, thus suggesting the diffusion of muscimol in the SC; the area never included the other hemifield, suggesting that the diffusion was limited to one SC. One of the monkeys became unable to make any saccades to the affected area.

3. Saccades to visual targets following injection of muscimol had longer latency and slightly shorter amplitudes that were corrected by subsequent saccades. The most striking change was a decrease in the peak velocity of the saccade, frequently to less than half the preinjection value.

4. Saccades to remembered targets following injection of muscimol also showed an increase in latency and decrease in velocity, but in addition, showed a striking decrease in the accuracy of the saccades. The trajectories of saccades became distorted as if they were deflected away from the affected area.

5. After muscimol injection, the area over which spontaneous eye movements were made shifted toward the side ipsilateral to the injection. Saccades toward the contralateral side were less frequent and slower. In nystagmus, which developed later, the slow phase was toward the contralateral side.

6. In contrast to muscimol, injection of bicuculline facilitated the initiation of saccades. Injection was followed almost immediately by stereotyped and apparently irrepressible saccades made toward the center of the movement field of the SC cells at the injection site. The monkeys became unable to fixate during the tasks; the fixation was interrupted by saccadic jerks made to the affected area of the visual field and then back to the fixation point.

7. After bicuculline injection, eye position shifted toward the side contralateral to the injection, and saccades to the contralateral side increased in frequency. In subsequent nystagmus the slow phase was toward the ipsilateral side.

8. These experiments indicate that GABA has a powerful effect on the SC; potentiation or reduction of GABA inhibition alters the execution of saccadic eye movements. They emphasize that the SC influences the velocity of saccadic eye movements in addition to their latency and accuracy.

INTRODUCTION

It is well established that the superior colliculus (SC) in the monkey is related to initiation of saccadic eye movements (see...
Cells in the intermediate layers discharge before saccadic eye movements (46, 49, 55). Each cell has its own movement field (49, 55); the cell discharges only before saccades with a particular range of directions and amplitudes. Most SC cells increase their discharge rate before saccades made under any condition (to visual targets, spontaneously in the light or dark), whereas other cells discharge only before saccades made to visual targets (36). Cells in the intermediate and deeper layers of the SC have direct projections to the brainstem reticular formation (16) where preoculomotor burst neurons are located (29, 34).

We have recently proposed that the saccade-related cells within the SC are under tonic inhibition exerted by cells in the substantia nigra pars reticulata (SNr), an output pathway of the basal ganglia. In previous studies (19-22) we found that a substantial number of SNr cells have activity correlated with saccades or visual stimuli. These SNr cells usually discharge with high frequencies, but this discharge is reduced before a saccade made under appropriate conditions. The decrease in discharge is contingent upon the conditions under which saccades are made, i.e., saccades made to visual targets or saccades made to the location of a target briefly presented and then remembered. Saccades made spontaneously in light or dark are not accompanied by a modulation of the tonic high discharge rate in the SNr. We found that these visual- or saccade-related SNr cells project to the intermediate layers of the ipsilateral SC because most of them were antidromically activated by stimulation of the SC. A decrease in SNr cell activity is correlated with an increase in SC cell activity to which the SNr cell is likely to project. These observations led us to the hypothesis that SNr cells tonically inhibit saccade-related SC cells, but before saccades to visual or remembered targets, these cells briefly reduce that inhibition. Reduction of inhibition allows a burst of spikes of the SC cells that, in turn, leads to the initiation of saccadic eye movements.

Figure 1 shows the logic of this study. Muscimol (a GABA agonist) injected locally into the SC should artificially enhance the inhibitory effects that are normally exerted by the SNr. Bicuculline (a GABA antagonist), on the other hand, should block any inhibitory inputs (indicated in black) with high discharge rate (indicated by thick axons) impinge on superior colliculus (SC) neurons that in turn project to brainstem oculomotor neurons (BS). Injection of muscimol into an area (indicated by stippling) should reduce the activity of SC and BS (indicated by thin axons) and reduce efficiency of saccades to the area of the field served by these cells. Injection of bicuculline should increase SC and BS activity (as indicated by thick axons) and facilitate saccades.
tory effects of the SNr on the SC. We find that these injections do disrupt saccadic eye movements; saccades are suppressed by muscimol and facilitated by bicuculline. The subsequent study (24) will directly address the question of whether these effects result from the action on GABAergic fibers from the SNr or those from some other source. Preliminary results have been reported (23, 57).

METHODS

These experiments required three methodological steps: 1) training monkeys to make saccades to visual or remembered targets; 2) locating and injecting a specific area within the SC; and 3) analyzing the oculomotor deficit.

Behavioral tasks

Two monkeys (Macaca mulatta) were first trained to fixate on a small spot of light on a tangent screen (53). Briefly, if the monkey touched a bar on the chair, a small spot of light (the fixation point) came on at the center of a screen in front of him. After a random period of time, this light spot dimmed. The monkey's task was to detect the dimming and release his hand from the bar within 0.4 s to receive a drop of water. Throughout the training and experiments, the monkey's weight was checked each day, and supplemental water and fruit was provided as needed. The monkey sat in a primate chair during the experiment and was returned to his home cage each day after the experimental session.

We then trained the monkeys on the two specific tasks designed to elicit saccades to visual targets (visually evoked saccades) and to remembered targets (memory-evoked saccades) (19, 21). Throughout the performance of these tasks, eye movements were measured by use of the magnetic search coil technique (39). The initial part of both tasks was identical to the fixation task described above, with the additional requirement that the fixation period did not begin until the monkey's eye position was within a position window, usually ±2°, centered on the fixation point.

In the saccade task, designed to elicit saccades to visual targets (Fig. 2A, upper), the fixation point (F) went off after a random period between 2.0 and 2.5 s, and another spot of light came on at the same time. This new spot (the target point, T) dimmed for 0.4 s after a random period between 0.5 and 2.5 s, and the monkey had to remove his hand from the bar in order to obtain the reward. This task required the monkey to move his line of sight from the fixation point to the target point as quickly and as accurately as possible to detect the dimming of the target. The target was projected onto the screen by reflecting the spot of light off a mirror driven by a galvanometer under computer control. Successive trials were separated by an interval of 1.5 s.

We used a standard list of 20 target positions with eccentricities from the fixation point up to 30° and a supplemental list of other points falling around the area of the expected deficit making a total of 25–35 positions. Each target position was presented twice, and the target points were chosen randomly from those targets that had not been already presented two times. A block of trials was composed of between 50 and 70 trials (2 trials for each of 25–35 target points), and each took 5–7 min to complete. This number of trials for each point represented a compromise between minimum change in behavior during a block of trials and maximum number of trials at each point. We selected this number of target positions because within the period of time required to test this number, we did not see any substantial changes in the monkey's oculomotor behavior even after an injection of muscimol or bicuculline.

The delayed saccade task was designed to elicit memory-evoked saccades (Fig. 2B, lower). Five hundred milliseconds after the monkey began to fixate, one of the target points (T, again chosen at random) was turned on briefly (50 ms). The monkey was required to continue to fixate for another 3 s while the fixation point (F) remained on; failure to do so terminated the trial. After the fixation point went off the monkey was free to make a saccade to the location of the flashed target. After 600 ms the same target point that had been flashed previously (T) was turned on again. The target dimmed after a random period between 0.4 and 1.0 s, and the monkey had to
respond during the 0.4-s dimming period in order to obtain a reward. If he waited for the target point to come on again and then made a saccade to the target, it was difficult to detect the dimming of the target after only a brief period of fixation. We used blocks of trials identical to those used in the saccade task.

Since the target point had been flashed briefly while he was fixating, the monkey's task was to make a saccade to the "remembered position" of the target. We could have rewarded the monkey for making correct saccades to the target (by using the eye-position recording) rather than requiring him to detect the dimming of the target. The advantage of our paradigm was that it rewarded the monkey for doing the task rather than for making a saccade of a given amplitude, which was one of the variables we were measuring. The paradigm also allowed the monkey to compensate for any error in eye position by making corrective saccades after the initial saccade. Without such compensation the monkey's behavior might have been disrupted when the muscimol or bicuculline began affecting his eye movements. During the experiment we also changed the size of the position window at the fixation point, depending on the effects of the injections, so that the monkey could complete a block of trials.

The background illumination on the tangent screen 58 cm in front of the monkey was 1 cd/m², and the monkey's view of the screen was unobstructed for the central 90° on the horizontal and vertical meridians. The fixation point and the target point were 0.2° diam and were 0.8–1.2 log cd/m² above background. The points were produced by projecting light-emitting diodes (LED, MV5352) with nearly instantaneous rise and fall times. The projection system consisted of the LED light source, a pinhole aperture (produced by a microelectrode poked through aluminum foil), and a projector lens.

**Injection of muscimol and bicuculline**

Under general anesthesia (pentobarbital sodium) monkeys were implanted with a head holder for restraint of the head during experiments, a stainless steel cylinder for microelectrode recording (8, 9), and an eye coil for measurement of eye position (11, 27, 39). Descriptions of these procedures are in Hikosaka and Wurtz (19). After surgery, monkeys were given analgesia for several days and allowed to recover for at least a week.

We first localized the area of interest within the SC using a glass-coated platinum-iridium microelectrode that penetrated through the dura. After removing this microelectrode we inserted a stainless steel guide tube (19 gauge, 30–40 mm long). One end of the guide tube was beveled so as to be easily introduced through the dura, and the tip of the guide tube was set ~5 mm above the SC. The guide tube was anchored to the inner wall of the cylinder by use of dental acrylic cement. Insertion of the guide tube was performed while the monkey was under ketamine hydrochloride (0.3 ml of 100 mg/ml). We applied antibiotic ointment to the top of the guide tube and plugged it with another stainless steel tube. We saw no sign of infection either on the surface of dura or at the end of the guide tube (on histological sections of the brain).

Our device for pressure injections was a glass pipette connected to a Hamilton syringe (5 μl) by polyethylene tubing. Fixed inside the glass pipette was a tungsten microelectrode (Frederick Haer) 50 μ OD; its tip protruded from the tip of the glass pipette by 100–200 μ. This combination of glass pipette and metal electrode allowed us to record single-cell activity related to saccadic eye movements, to apply electrical stimulation to produce saccades, and to inject drugs into the area.

The pipettes were constructed by pulling a 3-mm-diam glass tube in two steps. The first step was manual pulling that produced a thin tube about 1 mm diam; the second step used an automatic pipette puller to produce the tip. We broke the tip back until its diameter was 30–50 μ. After filling the lower section of the pipette with mineral oil, we inserted the tungsten microelectrode until its tip protruded from the glass pipette by 100–200 μ. The microelectrode was then cemented to the inner wall of the top of the glass pipette. The top portion of the microelectrode was bent down along the outer wall of the glass pipette so that polyethylene tubing could be slipped over the electrode wire and the pipette. The top of the glass pipette was filled with mineral oil as was the polyethylene tube, and any air bubble at the connection was eliminated. The connection between the pipette and the polyethylene tube was sealed with fast-drying cement.

Before each injection a drug solution was drawn into the pipette by using a 1-cc syringe attached to the polyethylene tubing. This syringe was replaced by a 5 μl Hamilton syringe just before the pipette was introduced into the brain. The pipette was held by the micromanipulator that was attached to the implanted cylinder and was lowered into the brain through the guide tube. We confirmed the area of the SC and the depth within it by recording cell activity through the tungsten microelectrode.

An injection of muscimol or bicuculline was done in several steps (0.2 μl for each step) with at least 30 s between steps. A successful injection was indicated by a temporary silencing of neural activity recorded through the tungsten microelectrode as the injection started. This was presumably because of the physical displacement of surrounding neural tissue away from the pipette tip by the
solution. Confirmation of an injection was critical; in some cases there was no output with the first several steps of the injection, and without this monitoring of neural activity we would have falsely assumed that an injection had occurred. We generally made injections in different areas of the SC at intervals of several days.

We used a GABA agonist, muscimol (Sigma), and a GABA antagonist, bicuculline methiodide (Sigma). They were used as a solution in saline with a concentration of 0.2, 1.0, 5.0 µg/µl. The amount of solution injected ranged from 0.4 to 2.0 µl. The pH of the solution was adjusted to 7.3. To verify that the change in eye movements was due to the injection of these chemicals, we made an injection of saline into the intermediate layers of the superior colliculus (see Table 1). No effect on eye movements was detected.

After injection of muscimol, bicuculline, or saline, we were able to record apparently normal cell activity through the same guide tube on the day after an injection. These observations suggest that our drug injections produced no severe structural damage to the cells. In addition, at the end of the series of experiments, the monkeys were perfused with normal saline and then 10% formaldehyde. Frozen sections (50 µ thick) of the SC were stained with cresyl violet for cells, and with the Weil method for fibers. Examination of these histological sections confirmed the absence of damage by the pipettes (Fig. 14). The pipette was withdrawn within 1 h after the injection was made.

After the injection (as well as before), blocks of trials for saccades to visual targets and to remembered targets were alternated. Spontaneous eye movements were sampled between these blocks of trials.

**Analysis of eye movements**

The behavioral tasks, as well as storage and display of data, were controlled by a real-time experimental system (REX) that operated on a PDP 11-40 computer and that was developed in our laboratory by Hays, Richmond, and Optican (17). We sampled and stored horizontal and vertical eye position every millisecond for periods lasting 1,023 ms. In the saccade task or the delayed saccade task this storage period started 50 ms before the offset of the fixation point. For some blocks of trials on the delayed saccade task we stored a series of such periods starting at the time of the flashed target and lasting 1,023 ms after the offset of the fixation point. Spontaneous eye movements were sampled every ms during the series of 1,023-ms storage periods usually separated by a period of 500 ms. The resolution of the analog eye-position signal was usually 0.1°.

We displayed the eye-movement records as superimposed horizontal and superimposed vertical eye-movement traces to see the temporal changes in saccades (e.g., Fig. 4). We displayed multiple eye movements as a vector display on an X-Y plane to see changes in the trajectory of saccades (e.g., Fig. 7). The position and direction of the spontaneous saccades were most clearly demonstrated on the vector display.

Quantitative analysis of saccades made to visual or remembered targets used a program developed by L. Optican. The program was modified to determine the onset of saccades, peak velocity, and the end of saccades. Saccade onset was defined as the time at which eye velocity exceeded 0.125 of peak velocity found in that saccade. The end of the saccade was defined as the time at which eye velocity fell below 1 degree/s. We used this latter criteria (which included post-saccadic drift as part of the saccade) because the measure remained consistent in spite of changes in saccadic trajectory after muscimol injections. Each record was verified by one experimenter by looking at a visual display of eye position and velocity that showed the time of the marked saccade characteristic.

Latency of the saccade (onset of the saccade minus offset of the fixation point) was determined from the prime component of a saccade. For target positions up to and including those with an angle of 45° from the horizontal, the horizontal component of the eye movements was used as the prime component; for the remaining targets, the vertical component was used as the prime component. Saccadic amplitude (eccentricity of eye position at the end of the first saccade) and final eccentricity of eye position (position at the end of the record, 973 ms after the offset of fixation point) were derived by use of both horizontal and vertical eye position information. Peak velocity was determined using both horizontal and vertical velocity at the time of the peak velocity of the prime component.

The quantitative data were printed in tables and then displayed on polar plots of the visual field (e.g., Fig. 5). Data for a given set of saccades were plotted at the target point of those saccades. Most values shown are the average of two trials (for the reason described in METHODS); an occasional trial was lost, usually due to the monkey's behavior or failure in data storage, and only one trial is shown at those points. This occurred at no more than two points per graph.

**RESULTS**

**Effects of muscimol injection**

Muscimol injected into the SC severely impaired the initiation and execution of saccadic eye movements. Figure 3 shows the sequence of steps followed in making an injection of muscimol and the time course...
of the effect as indicated by the change in latency of saccades to visual targets. At the beginning of the experiment the injection pipette was introduced into the left SC, and its tip positioned at the depth where cells recorded by the tungsten microelectrode protruding from the pipette showed a burst of discharges before the onset of saccades. Figure 3A shows a histogram of such a cell discharge after onset of the targets. The cell's discharges preceded only right-downward saccades, and the movement field of this cell is illustrated on the polar coordinate plot in Fig. 3A, right. Electrical stimulation through the tungsten electrode evoked right-downward saccades with a low threshold (9 μA in this case); their end point is indicated by the asterisk in Fig. 3A, right.

Figure 3B left shows superimposed traces of saccades made to targets in the lower right quadrant after the injection pipette was introduced into the left SC, but before injection. Figure 3B, right, shows the difference between saccade latencies obtained in this recording and those obtained before the pipette was introduced into the brain. Only the saccades to four target points in the lower right quadrant in the middle of the movement field of the cell showed any increase in latency. This probably resulted from leakage of muscimol from the pipette.

A successful injection of muscimol was indicated by a decrease in background neural activity. In Fig. 3C, beginning 3 min after pressure injection of muscimol, the latency of most saccades made to targets on the lower right (used as an index of the injection effect) increased by as much as 650–850 ms over the latencies obtained before the pipette was in the brain. But the area over which the latency increase occurred was still limited to the movement field of the cell (compare Fig. 3C right with Fig. 3A right). In Fig. 3D, 40 min after the injection, the monkey was almost completely unable to make saccades to the lower right field. The area of latency increase now included the upper right quadrant, but leftward saccades were fairly normal. The monkey also could not fixate accurately (as seen in the spread on the traces of Fig. 3D, left). After this stage, the eye started drifting slowly to the right, the drift became faster, and finally took the form of horizontal nystagmus with slow phases to the left and quick phases to the left. The monkey could not fixate and therefore could not perform the task, but showed no sign of discomfort. When the nystagmus subsided the monkey became able to perform the task again. Figure 3E shows that, 7 h and 45 min after the injection, the monkey was able to make saccades with only a slight increase in saccadic latency. Examination of the monkey's saccadic eye movements on the day following the injection showed no evidence of lasting effects.

The sequence of affected field areas shown in Fig. 3 indicated that the effects of muscimol were largely limited to the left SC. No injection showed any sign of diffusion of the chemical to the other side of the SC; saccades into the ipsilateral hemifield remained virtually intact 10 h after the injection. The diffusion area, however, definitely expanded over time, as demonstrated in Fig. 3, but there was no indication that it expanded beyond the colliculus. The injection site was located in the lateral part of the left SC (as illustrated in Fig. 14A). The lateral part of the SC is related to downward saccades (as in Fig. 3A), whereas the medial part is related to upward saccades. Therefore, the expansion of the affected area shown in Fig. 3 can be described in topographical terms; distribution of muscimol was largely restricted to the lateral part of the SC 3 min after the injection, was still higher in the lateral part, but had diffused into the medial part 40 min after the injection, and finally was nearly uniform in the left SC 7 h, 45 min after the injection.

Table 1 summarizes the five injections of muscimol made and the area of the movement field where saccades were affected. We present separately the effects on visually guided saccades and memory-guided saccades using primarily one injection (j221), since results of the injection are typical of the consistent effects obtained across injections.

**PARAMETERS OF EFFECTS ON SACCADES TO VISUAL TARGETS.** Figure 4 illustrates the effects of an injection of muscimol (j221) into the right SC that affected saccades made into the left visual field. Stimulation through the injection pipette evoked saccades that were toward the left with amplitudes of about 10° (Fig. 4A, left). The activity of multiple neurons recorded through the tungsten elec-
FIG. 3. Time course of changes in eye movements following an injection of muscimol in the left SC of monkey.

A: Activity of a single SC cell at the injection site. Left shows an averaged poststimulus time histogram for the
cell when monkey made saccades to targets in lower right quadrant of the visual field. Vertical line indicates when
fixation point went off and target point came on; height of ordinate indicates 100 spikes/s per trial. Right shows the
MUSCIMOL AND BICUCULLINE IN SC

TABLE 1. Injections into superior colliculus

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Amount, µg</th>
<th>Conc., µg/µl</th>
<th>Injection No.</th>
<th>Side</th>
<th>Stim. Thres. for Saccade pre/post, µA</th>
<th>Movement Field</th>
<th>Direction and Amplitude</th>
<th>Time Course, 1st sign/start recovery</th>
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<tr>
<td>Muscimol</td>
<td>2</td>
<td>1</td>
<td>j212</td>
<td>L</td>
<td>7/14</td>
<td>R &amp; D, 20°</td>
<td>1 min/7 h</td>
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<td>4</td>
<td>5</td>
<td>j221</td>
<td>R</td>
<td>22/32</td>
<td>L, 10°</td>
<td>&lt;6 min/&gt;9 h</td>
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<tr>
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<td>1</td>
<td>j228</td>
<td>R</td>
<td>18/42</td>
<td>L, 8°</td>
<td>&lt;14 min/7 h</td>
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<td>1</td>
<td>b3</td>
<td>L</td>
<td>9/19</td>
<td>R &amp; D, 10°</td>
<td>3 min/7.5 h</td>
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</tr>
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<td>1</td>
<td>b5</td>
<td>L</td>
<td>10/17</td>
<td>R &amp; D, 10°</td>
<td>&lt;7 min/&gt;2.5 h</td>
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<tr>
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<td>&lt;3.8</td>
<td>1</td>
<td>j207</td>
<td>L</td>
<td>25/13</td>
<td>R &amp; U, 70°</td>
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<td>1</td>
<td>j218</td>
<td>R</td>
<td>7/†</td>
<td>L &amp; U, 0.5°</td>
<td>6 min/3.5 h</td>
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<td>1.2</td>
<td>1</td>
<td>j233</td>
<td>R</td>
<td>7/†</td>
<td>L, 10°</td>
<td>&lt;7 min/1 h</td>
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<tr>
<td>Bicuculline</td>
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<td>1</td>
<td>j232</td>
<td>R</td>
<td>16/26</td>
<td>L &amp; U, 5°</td>
<td>&lt;1 min/&gt;5.5 h</td>
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<td>Saline</td>
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<td>b7</td>
<td>L</td>
<td>1/5</td>
<td></td>
<td>R &amp; D, 10°</td>
<td>7 min/50 min</td>
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</tbody>
</table>

L, left; R, right; U, up; D, down. j, First monkey, b, second monkey. † Not measured.

trode showed a burst of activity before the monkey made a leftward saccade whose amplitude and direction were similar to that of the stimulus-evoked saccade. Saccades evoked by electrical stimulation of the SC after injection of muscimol had reduced amplitude and slightly decreased velocity (Fig. 4A, right). The threshold increased from 22 µA before the injection to 32 µA after the injection, but latency showed no constant change.

Figure 4B shows saccades to visual targets made before (PRE) and after (POST) the injection; superimposed are two saccades made to each of six target points located at 5, 10, and 20° on the horizontal meridian on each side of the fixation point. Horizontal eye position is shown on the upper trace, vertical position on the lower trace. Before the injection (Fig. 4B, PRE), the saccades to each target point on the right (upward deflection) and the left (downward deflection) were remarkably consistent. Effects on eye movements became apparent within a few minutes after the injection (Fig. 4B, POST; 6 min after injection). Saccades to the three points in the left visual field (contralateral to the side of the colliculus injected) invariably had longer latencies and lower velocities than those before the injection. In contrast, no apparent change was seen in saccades made to the right (ipsilateral) visual field.

Figure 5A shows quantitative values for the differences between pre- and postinjection latency and velocity of saccades made to points throughout the visual field. The visual field is again represented in polar coordinates, and the mean value of the difference between the two saccades made to the target points before and after the injection is indicated by the height of the bar at the points. A difference is evident for saccades to targets in an area of the left visual hemifield. Latencies of these

movement field of the SC cell plotted on a polar plot of the visual field. Eccentricities of dashed circles are 5, 10, 15, 20°. R, L, U, D, right, left, up, and down, respectively. Difference in number of spikes in the posttarget period (0–400 ms after target onset) and that in the pretarget period (0–400 ms before target onset) was calculated for each trial and plotted at target position. Each data point is average of two trials. Asterisk indicates end point of stimulation-evoked saccades (threshold 9 µA). B–E: sequential change in saccades to visual targets before and after muscimol injection. B: data obtained after injection pipette was introduced into left SC but before muscimol was pressure injected. Left shows superimposed traces of saccades to targets in lower right quadrant; upper trace, horizontal eye position; lower trace, vertical eye position. Right shows changes in latency of saccades compared with those before the pipette was introduced into the brain. Increase in latency is upward. C–E: data obtained beginning 3 min (C), 40 min (D), and 7 h, 45 min (E) after muscimol was pressure injected. D shows that monkey could not make any saccade to most targets in lower right quadrant within the recording time (975 ms after target onset); in those cases the latency was assigned the maximum of 975 ms for calculation of mean latency. Injection site is shown in Fig. 14A.
FIG. 4. Effects on saccades following injection of muscimol into the right SC of monkey j. A: saccades evoked by electrical stimulation in the right superior colliculus before (left, threshold 22 μA) and after (right, threshold 32 μA) injection while monkey was looking at fixation point in center of screen. Stimulation was a train of biphasic, negative-positive pulses (200 Hz, 50 ms) with each pulse 0.2 ms. Vertical line indicates the onset of stimulation. B: saccades to visual targets (saccade task) before (PRE) and 6 min after (POST) injection of muscimol. Records for two saccades to each of 3 different points on right horizontal meridian (5, 10, and 20°) and 3 on left horizontal meridian are superimposed. Vertical line indicates time when fixation point went off and target point came on. C: saccades to remembered targets (delayed saccade task) before (PRE) and 11 min after (POST) injection of muscimol in right SC. Same saccade targets as in B. Left and right vertical lines indicate offset of fixation point and onset of target point, respectively. On one trial in POST the monkey made a saccade to the wrong side; instead of a saccade 10° left, the saccade was to right and then back to left near the end of trace. For A, B, C, and subsequent figures, upper traces are horizontal eye positions (right is upward and left is downward) and lower traces are vertical eye positions (up, upward; down, downward). Data shown in Figs. 4–7 were obtained after this injection of muscimol (j221), and site of injection is shown in Fig. 14B.

saccades after the injection (which ranged from 200 to 570 ms after, compared with 200 to 280 ms before) are sometimes twice as large as preinjection values and represent an increase of up to 300 ms (Fig. 5A, upper). Figure 5A also shows the amplitudes of first saccades (Fig. 5A, middle) and the final eye position (Fig. 5A, lower) for targets throughout the visual field. Leftward saccades became slightly shorter. Final eye positions were vir-
FIG. 5. Differences in parameters of saccades to visual targets (A) and remembered targets (B) before and after injection of muscimol in the right SC. Changes in these parameters are shown for saccades made to target positions indicated on polar plot of visual field. Increase is plotted upward, decrease downward. Eccentricities of dashed circles are 5, 10, 15, 20°. R, L, U, D are right, left, up, and down, respectively. Each point is the average of two trials.

MUSCIMOL AND BICUCULLINE IN SC

The postinjection velocity for saccades to the left was frequently less than half of the preinjection velocity, but no such consistent change was seen for saccades made to targets

tually unchanged; the monkey could reach the targets after corrective saccades.
on the right. Figure 6A shows the decrease in velocity of saccades made just to the affected area of the visual field. The peak velocity of the first saccade made to the target is plotted against the amplitude of that saccade.

The effect of muscimol on saccades to visual targets was generally less severe for this monkey (j) than for the other monkey (b). This monkey was always able to make saccades to the visual target while the other monkey was sometimes unable to do so (as in Fig. 3D). This difference may be related to the extensive overtraining that monkey j had received compared with the relatively small amount of training received by monkey b.

EFFECTS ON SACCADES TO REMEMBERED TARGETS. Muscimol injected into the SC disrupted saccades to remembered targets more severely than saccades to visual targets. Figure 4C shows superimposed traces of saccades made in the delayed saccade task to the same six target points on the horizontal meridian as shown in Fig. 4B. In the delayed saccade task (Fig. 2B), a target point was turned on briefly (50 ms), but the monkey was required to continue to fixate until the fixation point went off 3 s later (Fig. 4C, left vertical line). Because there was no target when the monkey made the saccade, the saccade depended entirely on short-term memory of target location. The target reappeared (Fig. 4C, right vertical line) about 600 ms after offset of the fixation point. Before the injection of muscimol (Fig. 4C, PRE) the monkey was able to make saccades to remembered targets which brought cyc position close to the target position (Fig. 4C, PRE), as indicated by the relatively small corrective saccades made after the target reappeared. Compared with visually evoked saccades (see Fig. 4B, PRE), the saccades here had slightly longer latencies with more scatter and lower velocities.

Records in Fig. 4C (POST) were taken 11 min after the muscimol injection in the right SC and show both a striking inaccuracy and reduced velocity of leftward saccades. The first saccades usually fell far short of target positions, as indicated by the large saccades correcting eye position after the targets reappeared. These corrective saccades were, however, visually evoked, and had higher velocities than the just-preceding saccades to remembered targets.

Figure 5B shows quantitatively the changes in parameters for saccades to remembered target points throughout the visual field and shows again that the deficits were largely restricted to targets in the contralateral hemifield. An increase in latency for leftward saccades is evident (Fig. 5B, upper), but the increase is not as consistent as for visually evoked saccades (Fig. 5A). This lack of consistency is due in part to the greater variability in saccadic latencies in the delayed-saccade task and in part due to the monkey's tendency to make saccades in the wrong direction (as illustrated in Fig. 7).

Probably the most striking effect of muscimol on saccades to remembered targets was the reduced accuracy of saccades. In Fig. 5B (middle) the amplitude of the first saccades was reduced for most target points in the left hemifield. The decrease in amplitude was as large as 15°. Furthermore, these errors in target acquisition remained to the end of the trial as indicated by the large differences in final eye position (as large as 11°, Fig. 5B, lower). Thus the error in eye position persisted for at least 400 ms after the target had reappeared. This is not surprising because the visual target was then present, the saccade that occurred would be a visually evoked saccade, and, as seen earlier, the latency of the saccades is increased.

The inaccuracy of the saccades is more clearly seen by looking at the trajectory of the saccades. Figure 7A shows the trajectory of saccades following stimulation, and Fig. 7B shows the trajectories of the first saccade made after offset of the fixation point. Before the muscimol injection (Fig. 7B, PRE) trajectories of saccades to the right and left were similar. After the injection (Fig. 7B, POST) they became distorted as if they were compressed from the left side. Leftward saccades were fewer in number (due to incorrect saccades to the right), very short and slow (as indicated by the closeness of the dots), or curved upward. Vertical saccades tended to curve to the right side. In contrast, saccades made to visual targets after muscimol injections became only slightly curved and ended near the target.

In addition to being inaccurate, the saccades that were made also had a decreased
FIG. 6. Peak velocities of saccades to the contralateral side before (filled circles) and after (open triangles) injection of muscimol. Saccades to visual targets in A, and saccades to remembered targets in B. Saccades were those made toward targets in area of visual field most affected by injection: between 135 and 225° of polar angle in A and between 157 and 225° in B with 0 being right, 180° being left. Amplitude and peak velocity of saccade are determined by use of both horizontal and vertical components. Long dashed regression line in B is for saccades to visual targets before injection to allow comparison between saccades to visual and remembered targets.
FIG. 7. Trajectories of saccades to remembered targets before (PRE) and after (POST) the injection of muscimol in right SC shown on a vector display. A: saccades evoked by electrical stimulation before injection; same stimulation records as in Fig. 4A. B: saccades to remembered targets with eccentricities of 5, 10, and 20° before (PRE) and after (POST) the injection. Length of each side of the square (distance between two corner angles of square) is 40°. Time interval between dots is 2 ms. Eye positions are displayed for period from offset of fixation point to end of first saccade. Two saccades are superimposed for each target point. Closer spacing of dots after the injection (POST) indicates lower-velocity saccades.
velocity as seen in Fig. 6B. Note that saccades to remembered targets even before the injection had a lower velocity than did saccades to visual targets (long dashed regression line in Fig. 6B is for the visually evoked saccades in 6A; see also Fig. 11 and Ref. 24).

EFFECTS ON SPONTANEOUS EYE MOVEMENTS.

We recorded eye movements either in light or in total darkness while the monkey was not performing any task, and Fig. 8 shows an example of the changes occurring in eye movements under these conditions (spontaneous eye movements). Figure 8A shows the direction of the saccade following stimulation in the right SC, up and to the left. Spontaneous eye movements scanned both the left and right visual fields (Fig. 8B, + indicates primary position) and had generally similar characteristics.

The area scanned by the eyes 37 min after muscimol injection shifted to the right (Fig. 8C). The deviation was in the direction opposite to saccades evoked by electrical stimulation at the injection site. The eye moved in a small area on the right, the area did not include the center of the orbit, and the direction of gaze rarely crossed the midline to the left. Furthermore, leftward saccades were less frequent and much slower than rightward saccades (Fig. 8C). The monkey was, however, able to perform the tasks at this time.

A period of nystagmus (Fig. 8D) followed 3 h, 15 min after the injection. The quick phase was to the right, slow phase to the left. The area the eye scanned, however, remained on the right (Fig. 8D). The eye never crossed the midline. The monkey was now unable to perform the tasks because he could not fixate. When we presented him with a pellet of food from his left side, he was never able to look at it. Nonetheless, he was eager to eat the pellet and had no difficulty in eating. We could not detect any involuntary skeletal movements, nor could we feel involuntary contraction of neck muscles. The monkey showed no sign of discomfort. The nystagmus subsided usually within 1–2 h after onset.

Effects of bicuculline injection

In contrast to muscimol, injection of bicuculline into the SC facilitated the initiation
Fig. 9. Effects of bicuculline in left SC on saccades to visual targets. Left column shows superimposed horizontal and vertical eye-position traces, right column shows vector displays of eye position. A: saccades evoked by electrical stimulation in the left SC before injection. Monkey was not fixating on a light stimulus; eye position is shown as if saccades started from the same position. Threshold was 12 μA. B: saccades to visual targets before (PRE) and 1 h after (POST) an injection of bicuculline. On left, saccades to 4 different points on the vertical meridian are superimposed. Vertical line indicates time when fixation point went off and target point came on. On right, eccentricity of targets was 20°; eye positions are displayed only for period from offset of fixation point to end of first saccades. Note similarity of saccades with short latencies after the injection to stimulus-evoked saccades. Data shown in Figs. 9–11 were obtained following same injection of bicuculline methiodide into intermediate layers of SC.
FIG. 10. Saccadic jerks during the fixation period after bicuculline injection into left SC. A: superimposed traces of eye position during the fixation period of 8 trials of a delayed saccade task. Records start after target point was flashed briefly and end at offset of fixation point (vertical line). Upper traces are horizontal and lower traces vertical eye positions. Target eccentricity was 20°. B: trajectories of saccadic jerks during same fixation periods.

of saccades. A successful injection of bicuculline was followed by stereotyped and apparently irrepressible saccades made to the center of the movement field of SC cells near the injection site. As with muscimol injections, the results of bicuculline injections were highly consistent across injections so that we will concentrate on one injection (j214).

EFFECTS ON SACCADES TO VISUAL TARGETS. Figure 9 shows changes in visually evoked saccades following an injection in the left SC. In Fig. 9, the left column shows the
FIG. 11. Peak velocity of saccades to targets in lower right quadrant plotted against their amplitude before (filled circles) and after (open triangles) injection of bicuculline into left SC. A: saccades to visual targets. B: saccades to remembered targets. Whereas little change is evident in A, the velocity in B increased after injection nearly to that for visually evoked saccades.

Superimposed horizontal (upper) and vertical (lower) traces of eye position, and the right column shows a vector display of eye position. Electrical stimulation produced large, right-downward saccades (Fig. 9A, stimulation was done when the monkey was not fixating).
Figure 9B left shows saccades to visual targets on the vertical meridian before (PRE) and 1 h after (POST) the injection. Following the injection the monkey tended to make right-downward saccades in a direction similar to the stimulus-evoked saccades. Latencies were, frequently less than 100 ms. The monkey then corrected his "error" by making a saccade back to the fixation point or to the target.

The tendency to make right-downward saccades is clear in the vector display (Fig. 9B, right), which shows the trajectories of the first saccade after the target came on. After the injection the saccades were predominantly toward the right lower quadrant even when the target was not there. This pattern is opposite to that observed after injection of muscimol where trajectories were displaced away from stimulus-evoked saccades (see Fig. 7).

EFFECTS ON SACCADES TO REMEMBERED TARGETS. The inability to suppress saccades was particularly striking during the fixation period of the delayed saccade task (Fig. 10). After the target was flashed (at the beginning of the trace) the monkey broke fixation frequently by making saccadic jerks (Fig. 10A), which he never did before the injection. The trajectories of these irrepressible saccadic jerks (Fig. 10B) were quite similar to those of stimulus-evoked saccades (Fig. 9A, right). This pattern was probably one of the most sensitive measures for the effects of bicuculline in the SC. In fact, at this time after bicuculline injection (1 h, 15 min after the injection) gross deficits were not so obvious when actual targeting saccades were made.

QUANTITATIVE CHANGES. Figure 11 shows peak velocities of saccades to targets in the lower right quadrant following the same injection of bicuculline as shown in Figs. 9 and 10. The velocity of the saccades to visual targets (Fig. 11A) was virtually unchanged. For the saccades to remembered targets (Fig. 11B), however, the velocity was frequently increased substantially, nearly to the higher velocity seen for visually evoked saccades. The increase in velocity is particularly evident for saccades whose amplitudes were between 15 and 20°. Smaller saccades were fewer after the injection and showed no significant increase in velocity. This indicates that sac-
FIG. 13. Spontaneous saccades after an injection of bicuculline in center of right SC. A: saccades evoked by electrical stimulation. B: spontaneous eye movements recorded 7 min after injection. C: 24 min after injection. Left column shows trajectories of same eye movements on a vector display with primary position indicated by cross. Right column shows trajectories of saccades or quick phases aligned as if they started from center of orbit; numbers in each corner indicate no. of saccades that ended in that quadrant. Same injection as in Fig. 12.

Saccades with amplitudes similar to the stimulus-evoked ones were selectively facilitated and occurred with higher velocities.

If saccades to visual targets were directed in the wrong direction, as is the case for those shown in Figs. 9 and 10, it is not useful to compare quantitatively the saccades before and after an injection based on target positions. In order to show the effect of bicuculline on the latency, velocity, and amplitude of saccades in the absence of intrusive saccades, we quantified these changes for an injection.
that produced relatively mild effects, that is, few intrusive saccades (Fig. 12). Latencies of leftward saccades decreased, in some cases by more than 100 ms (Fig. 12, middle). The distribution of the latency decrease corresponded well to the movement field of a single cell recorded at the injection site (Fig. 12, upper). Amplitudes of leftward, large saccades generally became shorter (Fig. 12, lower).

**EFFECTS ON SPONTANEOUS EYE MOVEMENTS.** Changes in spontaneous eye movements were the first detectable effects of bicuculline. Figure 13 shows an example of an injection in an area of the right SC in which stimulation evoked saccades (Fig. 13A) that were about 7° long and to the left. The left column in Fig. 13 shows the trajectories of spontaneous irresspressible saccades, and the right column shows the saccades aligned as if they started at the center of the display. The injection was followed quickly by staircase saccades and Fig. 13B, right, demonstrates that the direction and amplitude of the components of the staircase were similar to the stimulus-evoked saccades. The eye stayed in an area close to the end point of the stimulus-evoked saccades (Fig. 13B, left). More saccades were made to the left than to the right (as indicated by number of saccades to each quadrant shown in the corner of Fig. 13B, right). About 24 min after the injection the eye started drifting to the right, as nystagmus developed (Fig. 13C). The slow phases of bicuculline-induced nystagmus in this case seemed directed toward a particular horizontal position; the eye deviated horizontally to the right to a point 7° from the midline without regard to vertical position. The horizontal position to which the eyes moved was the same as that reached by stimulus-evoked saccades. After other injections such a goal-directed effect was not as clear. An injection into the foveal area moved the eye position nearly to the lateral limit of the orbit.

The monkey was unable to fixate at this stage (Fig. 13C), but showed no sign of discomfort. We did not observe any involuntary skeletal movements or feel any involuntary contraction of the monkey's neck.

**FIG. 14.** Sites of injections into intermediate layers of the SC of two monkeys. Lesions were made by passing currents through tungsten-wire recording electrode. Mark on right (B) corresponds to 3 injections in first monkey (J221, J223, J228, see Table 1); mark on left (A) corresponds to all 4 injections in the second monkey (b1, b3, b5, b7, see Table 1). Scale marker is 1 mm.
muscles. Usually after 30–90 min the nystagmus subsided enough so that the monkey resumed performance of the behavioral tasks.

**Histology**

Near the end of this series of experiments we marked the sites of several injections by passing current through the metal microelectrodes. The marks were found to lie in the intermediate layers of the SC (Fig. 14). The mark in the left SC, shown in Fig. 14A, was made through the guide tube used for all four injections in one monkey (b1, b3, b5, b7 indicated in Table 1). As expected from the movement fields of cells at the injection site (right and down, see Fig. 3A, right), the lesion was found in the lateral part midway between the anterior and posterior poles of the SC. Similarly, the lesion shown in Fig. 14B, found in the central part of the right SC of the other monkey, was at the site of three injections (j221, j223, j228) where cells had movement fields centered 10° to the left. No apparent sign of infection or cell loss was noted at the marked injection sites.

**DISCUSSION**

Injections of GABA-related substances into intermediate layers of the monkey SC produced changes in eye movements. The two most striking effects of muscimol were a reduction in the velocity of saccades and inaccurate saccades to remembered visual targets. The most prominent effects of bicuculline were the irrepressible saccades. These effects of both muscimol and bicuculline were initially specific to the movement field of cells at the injection site. We will first discuss the action of muscimol and bicuculline on inhibition in the SC, then the role of the SC in the initiation of saccades, and finally the influence of the SC on velocity of saccades and eye position.

**Action of muscimol and bicuculline on inhibition in SC**

The hypothesis, on which our experiments are based, is that both a tonic and a phasic action of SNr on SC exist. Tonic inhibition sets the level of responsiveness of SC to excitatory inputs. Phasic pauses in this inhibition convey a signal for the initiation of saccades to visual targets or for those to remembered targets, but not for those made "spontaneously." This inhibition is presumably mediated by GABA.

Muscimol is known to be an agonist of GABA (3). It shows a remarkable selectivity in its interaction with GABA receptors, and has the same physiological effects as GABA (32); it increases the conductance of chloride ions through the cell membrane, which usually leads to hyperpolarization of the membrane. The effect is an inhibition of excitatory inputs. Muscimol, however, binds to GABA receptors with higher affinity than GABA itself (3), crosses the blood-brain barrier, and has been used for pharmacological studies mainly for these reasons.

Results of stimulation of the intermediate layers of the SC, as a measure of excitability changes of output cells in the SC, were consistent with the pharmacological evidence: threshold for saccade generation by electrical stimulation did not increase very much after the injection (see Table 1), whereas it became very high after injection of a local anesthetic (Hikosaka and Wurtz, unpublished observations). This suggests that the effect of muscimol on saccade generation was not due to its inhibitory action on impulse conduction; a slight increase in threshold would be expected due to the hyperpolarization of the membrane as well as the temporary displacement of neural tissues away from the electrode. The effect of the muscimol injections on control of eye movements therefore can be regarded as requiring greater synaptic drive to depolarize the SC cell membrane sufficiently to produce spikes.

Muscimol injected into the SC must act to increase the tonic inhibition on adjacent cells. These cells should require greater synaptic drive to activate them than do cells related to other parts of the visual field. The reduction in the number of spontaneous and evoked saccades made to the affected area of the visual field and the slowing of saccades are consistent with such an increase in inhibition. Muscimol must also block any phasic changes, largely eliminating the pauses in inhibition related to saccades to visual or remembered targets. Since saccades to remembered targets are greatly affected, probably the most important signal to the SC from the SNr is the pause in the tonic.
Inhibition preceding the memory-evoked saccade. In contrast, muscimol modifies saccades to visual targets to a lesser extent, thus suggesting that there is an alternate, possibly excitatory, input that is effective in spite of the increased tonic inhibition. For visually evoked saccades, both inputs probably are active normally, a decrease in inhibition and an increase in excitation, and this combination might be reflected in the higher velocity of saccades made to visual as opposed to remembered targets (Fig. 6B).

Bicuculline is now generally accepted as a selective GABA antagonist. It competes with GABA for common binding sites on GABA receptors, but has no direct action on the membrane of the postsynaptic cell (3). Bicuculline, therefore, would reduce chloride conductance and depolarize the cell membrane by reducing the effectiveness of tonic inhibitory input, but only if substantial GABA inputs were present. This is probably what we observed after injection of bicuculline into the SC; cells near the injection site would be depolarized, their membrane potentials would be shifted above the thresholds for initiation of action potentials, and therefore, repetitive saccades would be produced. This lowered threshold for the effectiveness of synaptic drive is consistent with the irresistible saccades made to the affected part of the visual field.

Bicuculline either reduces the tonic inhibition from SNr or artificially produces a pause in inhibition that could be a signal for a saccade to either a visual or remembered target. The effect in either case might be likened to a "phosphene", but a motor one rather than a sensory one. This phosphene at the site of the injection competes with the activity in other areas of the colliculus related to other saccade-related inputs. The phosphene clearly is more powerful than the signals related to remembered targets and to many visual targets, and even competes with visual fixation as indicated by the saccadic jerks occurring in all these cases.

While we have assumed throughout this discussion that muscimol and bicuculline acted on afferents to SC from SNr, these experiments do not distinguish between the action on afferents from SNr, or on other afferents or intrinsic connections within the SC. The following paper (24) addresses this question and shows that most of the effects seen here do result from altering the effect of SNr fibers going to SC.

Role of SC in initiation of saccadic eye movements

That the intermediate layers of the SC are involved in the initiation of saccades is undisputed. Electrical stimulation in the SC elicits saccadic eye movements in all mammals studied so far, e.g. monkey (41, 47), cat (25, 43, 50), rabbit (44), and rodent (35). Cells in the intermediate layers of the monkey SC discharge before a saccade (46, 49, 55). Each cell has its own movement field (49, 55): the cell discharges only before saccades with a particular range of directions and amplitudes. Cells in the intermediate layers of the monkey or cat SC project extensively to the dorsomedial pontomedullary reticular formation (7, 13, 16, 28, 38) where "burst neurons" are localized. These neurons are specifically related to saccades or quick phases (18, 26, 29, 34). The simple schema that emerges from these observations is that neural activity in the SC determines the vector of a saccade, and this signal is then sent to the brainstem oculomotor system.

This schema predicts that the removal of the SC would disrupt initiation of saccades. However, in previous studies the effects of such removal turned out to be slight. Some increase in latency of saccades has been reported consistently (1, 2, 37, 48, 56). Some decrease in frequency of spontaneous saccades has also been noted (1) as has some change in velocity (48, 56). These studies have not reported changes in direction of saccades, and slight changes in amplitude are indicated only by an increase in the number of corrective saccades (37). Although some studies report severe deficits in eye movements (33, 45) objective measure of eye movements was not provided. As pointed out in a previous paper (2) it was also possible that experimental lesions included other brain areas like the medio-dorsal thalamus which is also related to eye movements.

As we have indicated, muscimol should act in some ways like a surgical ablation, though briefly and reversibly, because it should act on GABA receptors of SC cells,
hypothesized, reduce the effectiveness of synaptic inputs, and suppress the spike activity of the cells. Unlike the previous surgical or electrolytic lesions, however, muscimol produced severe deficits in eye movements. This paradox might be explained by the ability of the brain to compensate over time for a partial dysfunction. In all of the previous studies, the SC was damaged physically, and oculomotor behavior was tested usually after a lapse of a day and frequently a week. Severe deficits may not have been observed because over time other brain areas compensated for some deficits in SC function.

The lowered velocity of saccades would presumably have been one such deficit for which compensation had largely occurred by the time previous investigators looked at the saccades. The increase in latency has been consistently seen previously, but it was more severe in the present experiments with muscimol. It was so severe in the less well-trained monkey (b in Table 1) that he was not able to make saccades toward the affected quadrant, even to a visual target. The better trained monkey (j) was able to make saccades to visual targets but with longer latencies. This suggests that the SC might be more important for a naive monkey to initiate saccades to visual targets and that other brain areas cannot then immediately substitute for the SC, but verification of such a difference in training would require tests on more than the two monkeys of our experiments. In summary, the SC is probably a more critical station for saccade-related signals destined for the brainstem oculomotor system than previous ablation experiments have indicated, but one for which substantial compensation for loss can be made.

Bicuculline, on the other hand, facilitated the occurrence of saccades with a certain range of directions and amplitudes that corresponded to the movement field of SC cells near the injection site. Latencies of the saccades to the affected area of the visual field in the two saccade paradigms can be <100 ms (Fig. 9). These saccades might correspond to “express saccades” observed by Fischer and Boch (10), which can be seen when a monkey makes a saccade with a gap in time between the offset of the fixation point and the onset of the target point. Bicuculline might be regarded as activating a short visuoculomotor pathway underlying the express saccades. In other words, the presumed GABA-mediated inputs normally suppress the express saccades that are frequently less accurate than the longer-latency saccades (10).

The GABA-mediated inputs, however, may have different roles in other species of animals. Kilpatrick, et al. (31) reported that GABA-related substances injected into the rat SC produced turning of the animal’s whole body, specifically, tight contraversive circling by picrotoxin and only occasional ipsiversive turning by muscimol. Although it is not clear whether these rats showed changes in saccadic eye movements, this comparison shows a change in the function of the SC across species. This issue will be discussed in more detail in the subsequent paper (24).

Role of SC in control of saccadic velocity and eye position

One of the most surprising findings of this study is the striking decrease in saccadic velocity after injections of muscimol into the SC. Some saccades had peak velocities near 100 deg/s, which fell within the range of smooth pursuit movements (40). In addition, bicuculline in the SC increased the velocity of saccades made to remembered targets, which are normally slower than saccades to visual targets. Such striking changes in saccadic velocity have not been documented following ablation of the SC although Wurtz and Goldberg (56) mentioned a slowing of saccades, and Schiller, True, and Conway (48) referred to a reduction in eye movement velocity. Instead the SC has generally been considered to control the vector of a saccade but not its time course (54).

Some idea of how the SC might influence saccadic velocity can be gained from considering the effect of the SC on brainstem cells related to the generation of horizontal eye movements. Saccadic velocity is well correlated with spike frequency of burst neurons (29, 30, 51, 58), and in order to alter velocity, muscimol in the SC must lead to a lowering of this spike frequency. Many cells in the intermediate layers of the SC project to the contralateral pontomedullary brainstem and terminate in the dorsomedial reticular formation (13). Stimulation of the SC has been
demonstrated to produce excitation in long-
lead burst neurons and pause neurons in
monkeys (38) and monosynaptic driving of
inhibitory burst neurons in cats (18). If SC
cells were hyperpolarized with high mem-
brane conductance, excitatory inputs, which
normally produce a high-frequency burst of
spikes, might drive the cell’s membrane po-
tential barely to the threshold of action po-
tentials. The SC cells and the brainstem burst
neurons would produce a sequence of spikes
with longer latency, lower frequency, and
with a smaller number, and this would affect,
directly or indirectly, the brainstem burst
neurons. This would result in a saccade with
a longer latency, lower velocity, and shorter
amplitude. In terms of the model of oculo-
motor control proposed by Robinson et al.
(42, 59), the superior colliculus would be
regarded as influencing the gain of the neural
pulse generator.

The effects of both muscimol and bicucul-
line on spontaneous eye movements were
also striking. Bicuculline-induced saccades
were almost identical with saccades evoked
by electrical stimulation. Although SC cells
would be continuously depolarized by the
blockade of GABA-receptor binding, resultant
eye movements were not continuous but
instead were a repetition of saccades. Repet-
titive saccades were also elicited by continuous
electrical stimulation (41, 47). These obser-
vations are consistent with evidence showing
that SC cell membrane has an intrinsic
mechanism to convert steady excitatory in-
puts to groups of action potentials (14).

If saccades with similar direction and am-
plitudes occurred repetitively, or if the eye
drifting predominantly in one direction, the
eye would naturally end up at the mechanical
limit of the orbit. Except for one bicuculline
experiment, in which the injection was near
the foveal region, we did not see such extreme
eye positions. Instead, we observed a strong
tendency for the eye to stay in the contralat-
eral hemifield, which is close to the end point
of stimulus-evoked saccades from the center.
A basically similar shift of eye position was
evident after muscimol injection, but in the
opposite direction; the eye stayed in an area
almost symmetrical to the end point of stim-
ulus-evoked saccades. The tendency to shift
eye position into a certain orbital position
became more evident when nystagmus ap-
peared, but some of these later effects may
result in part from spread of muscimol to
structures adjacent to the SC (such as the
mesencephalic reticular formation).

One explanation of these shifts in orbital
position is that the injections reduce (mus-
cimol) or increase (bicuculline) the proba-
bility of saccades of particular direction and am-
plitude. If the average orbital position of the
eye is, in part, a function of the probability
of saccades in various directions, markedly
changing the probability for one direction of
movement should change the average orbital
position. This change in probability in itself
might account for the shifts in orbital position
we observed. On the other hand, particularly
after bicuculline injection, slow phases of
nystagmus sometimes appeared goal-directed
for horizontal eye position. It is intriguing
that the goal was almost at the same hori-
zontal position as the end point of stimulus-
evoked saccades and this is reminiscent of
observations made with electrical stimulation
of SC in the cat (see for example Ref. 15).
Further observations on the relation of the
region of the SC injected, the position to
which the eye shifts, and the consistency of
the orbital-position shift would be required
before any conclusion can be drawn about
the mechanism of these shifts after bicuculline
and muscimol injections.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the conscientious care
of the monkeys by G. Snodgrass, the histological assistance
of G. Creswell and L. Cooper, and the secretarial assis-
tance of J. Steinberg and P. Brown. We are also grateful
for advice on analysis programs by L. Optican and J.
Shaw.

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Received 21 February 1984; accepted in final form 7
August 1984.

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