Fixation Cells in Monkey Superior Colliculus
II. Reversible Activation and Deactivation

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SUMMARY AND CONCLUSIONS

1. We tested the hypothesis that a subset of neurons, which we have referred to as fixation cells, located within the rostral pole of the monkey superior colliculus (SC) controls the generation of saccadic eye movements. We altered the activity of these neurons with either electrical stimulation or GABAergic drugs.

2. An increase in the activity of fixation cells in the rostral SC, induced by a train of low-frequency electrical stimulation, delayed the initiation of saccades. With bilateral stimulation the monkey was able to make saccades only after stimulation ceased.

3. Pulses of stimulation delivered during the saccade produced an interruption of the saccade in mid-flight. The latency to the onset of this perturbation was as short as 12 ms.

4. Injection of the γ-aminobutyric acid (GABA) antagonist bicuculline into the rostral pole of the SC, which decreases normal GABA inhibition and increases cell activity, increased the latency of saccades to both visual and remembered targets.

5. Injection of the GABA agonist muscimol into the rostral SC, which increases normal GABA inhibition and decreases activity, reduced the latency for saccades to visual targets. The monkey also had difficulty maintaining visual fixation and suppressing unwanted saccades.

6. After muscimol injections, monkeys frequently made very short-latency saccades forming a peak in the saccade latency histogram at <100 ms. These saccades are similar to express saccades made by normal monkeys. This finding suggests that the fixation cells in the rostral SC are critical for controlling the frequency of express saccades.

7. These results support the hypothesis that fixation cells in the rostral SC inhibit the generation of saccadic eye movements and that they form part of a system of oculomotor control, that of visual fixation.

INTRODUCTION

In the preceding article (Munoz and Wurtz 1993) we described a subset of cells located in the rostral pole of the monkey superior colliculus (SC) that were tonically active when the monkey fixated a target of interest and paused for saccadic eye movements. Similar characteristics had previously been described for a population of cells, located in the rostral SC of the cat, that projected to the region of the paramedian pontine reticular formation (PPRF) related to saccade generation (Munoz and Guillon 1989, 1991; Munoz et al. 1991; Peck 1989). Our hypothesis, like that developed for the cat (Munoz and Guillon 1991), is that fixation cells in the rostral pole of the SC are critical for maintaining active visual fixation and suppressing the generation of saccades.

To test this hypothesis of fixation cell function, we trained alert monkeys to perform fixation and saccade tasks, and then we artificially altered the activity of cells within this region of the SC. Figure 1 illustrates the logic of our experiments: we hypothesize that fixation (FIX) cells in the rostral pole of the SC exert direct control over the saccadic system by inhibiting the saccade (SAC) cells in the SC as well as by activating the brain stem omnipause neurons that gate the burst neurons in the PPRF (not shown). The inhibitory connections between FIX and SAC cells need not be direct as shown schematically in Fig. 1, nor need the SAC cells be restricted to the SC as we have shown for simplicity. We first increased the activity in the fixation cells by applying low-frequency electrical stimulation (Fig. 1B) to increase activity of cells adjacent to the site of stimulation. According to our hypothesis, this manipulation should lead to decreased activity of the saccade cells. Modulation of the activity of fixation cells can also be achieved by changing the effectiveness of the endogenous inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Andrews and Johnston 1979; Hikosaka and Wurtz 1985). An increase in activity results from local application of a GABA antagonist, bicuculline (Fig. 1C), which acts by reducing the normal inhibition due to endogenous GABA activity. This increased activity of the fixation cells might produce a decrease in activity in the saccade cells thereby making it harder for the monkey to initiate a saccade. A decrease in activity of the fixation cells follows injection of a GABA agonist, muscimol (Fig. 1D), which should make it harder for the monkey to suppress a saccade.

We find that, when fixation cells in the rostral pole of the SC are artificially activated with either microstimulation or injection of bicuculline, saccadic reaction times increase. In contrast, when the cells are artificially inhibited after a muscimol injection, saccadic reaction times are reduced, and monkeys lose the ability to suppress unwanted saccades. Both results support the hypothesis that the fixation cells inhibit the generation of saccadic eye movements.

Preliminary reports of some of these results have appeared previously (Munoz and Wurtz 1992).

METHODS

Monkeys were prepared for experiments by the use of the same procedures and the same series of fixation and saccade tasks described in the preceding article (Munoz and Wurtz 1993).

We electrically stimulated the rostral pole of the SC at sites adjacent to the location of physiologically identified fixation-related cells (Munoz and Wurtz 1993) in three monkeys (p, g, and a). We delivered stimulation through one of two types of elec-
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We injected muscimol (Sigma), bicuculline methiodide (Sigma), and sterile saline into the rostral pole of the SC in two monkeys (g and e) with the use of a previously described technique (Crist et al. 1988). The muscimol and bicuculline crystals were dissolved in saline. The injection syringe consisted of a 30-gauge needle fitted to a 10-μl Hamilton microsyringe and lowered through a guide tube to the depth that fixation cells were previously identified with single-cell recording and microstimulation. We injected between 0.3 and 2.0 μl of solution in 0.3- to 0.5-μl amounts every 30-60 s. Therefore each injection took no more than 2-3 min to complete. The concentrations and amounts of each injection are summarized in Table 1. We allowed the monkey at least 48 h for recovery before making another injection.

For each injection we collected pre- and postinjection data files. Each file contained data taken while the monkey performed four saccadic tasks (visually guided, memory guided, gap, overlap) (see Fig. 2 of Munoz and Wurtz 1993) to a given target presented 5 or 20° to the right and left. These eight conditions (4 tasks, 2 directions) were presented to the monkey in random order from a lookup table. The monkey had to correctly execute a predetermined number of saccades in each condition (usually 10 or 20) to complete a data file that consisted of 80 or 160 correct responses. Both correct and incorrect responses were saved for analysis, but the monkey was only rewarded for correct responses.

We obtained saccade characteristics (latency, amplitude, velocity, duration) during off-line analysis, with the use of a previously described computer program that identified the onset and termination of each saccade with the use of velocity and acceleration threshold criteria (Wattzman et al. 1991).

RESULTS

Stimulation of the rostral SC

We first tested the hypothesis that activity of fixation cells in the rostral pole of the SC modulates the occurrence of saccades by artificially increasing the activity of cells in this area via electrical stimulation (Fig. 1B).

DELAY OF SACCADIC INITIATION. Low-frequency stimulation (150 Hz) of the rostral pole of the SC delayed the initiation of saccadic eye movements in all three monkeys tested. Figure 2 illustrates the effect of stimulating both rostral poles

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* In monkey e, all injections were in the right rostral superior colliculus (SC); in monkey g, all injections were in the left rostral SC.
simultaneously while the monkey made saccades in the visually guided saccade paradigm. Stimulation trials (---) were interleaved with control trials when no stimulation occurred (· · ·). The small vertical tick on the eye position and velocity traces indicates the cue for the monkey to initiate the saccade (simultaneous offset of the fixation point and onset of the peripheral target). The monkey made saccades ~200 ms after target onset in the control condition to targets 20° to the left, right, up, or down. A long-duration, low-frequency train of stimulation (500 ms, 150 Hz, 30 μA, marked by the horizontal bar under the eye position traces) delayed saccade initiation to all targets. All centrifugal saccades were affected as were centripetal saccades (not shown). The monkey could only generate the saccade to the new target after the stimulation ceased. We found similar delays in saccade initiation with low-frequency stimulation of the rostral SC in all three monkeys.

Even with the delay in initiation, the saccades reached the target as indicated by the equal amplitude of the normal and delayed saccades in Fig. 2. This accuracy remained even if the target was no longer present after the stimulation ended as shown by the effect of stimulation when the monkey made a saccade to the remembered location of the target (Fig. 3). In this modified version of the memory-guided saccade task, the fixation point went off at the onset of a 50-ms target flash (marked by the small vertical tick), and in control trials the monkey looked immediately to the remembered location of the target flash. When we applied a long-duration train of stimulation (1 s, 100 Hz, 30 μA) immediately after the offset of the target flash, the monkey's saccade was delayed until after offset of stimulation. Despite the 1-s delay caused by stimulation, the monkey was still able to generate an accurate saccade even in complete darkness.

Stimulation of just one rostral pole also delayed the initiation of saccades. Figure 4 shows the results of unilateral stimulation at the same two electrode positions that produced the effects illustrated in Fig. 2. We stimulated either the left (Fig. 4, A and B) or right (Fig. 4, C and D) rostral pole while the monkey looked at targets located 20° left (Fig. 4, A and C) or right (Fig. 4, B and D). Saccades to targets that were located in the visual field ipsilateral to the SC stimulated (Fig. 4, A and D) began only after stimulation terminated. Saccades to the side contralateral to that stimulation (Fig. 4, B and C) were initiated during stimulation but were hypometric; the monkey only achieved fixation of the new target by generating a corrective saccade. We attribute this directional difference to an interaction between cells activated directly and indirectly by electrical stimulation (see DISCUSSION).

The delay in saccade initiation produced by stimulation of the rostral pole was evident with as little as 10 μA but was
FIG. 3. Suppression of saccades by bilateral stimulation during the memory-guided saccade task. Stimulation of both rostral poles simultaneously in monkey a. Five control trials (---) and 5 stimulation trials (----) are superimposed in each panel. In this modified memory task, the fixation point was turned off at the onset of the 50-ms target flash (marked by the small vertical tick on the position and velocity traces). The horizontal bar under the eye position traces marked the time of stimulation. The low-frequency, long-duration train (100 Hz, 1,000 ms, 30 μA) delayed leftward (A) and rightward (B) saccades. Note that the small saccades elicited during stimulation (see velocity traces) are in the same direction as the target flash and therefore not the result of stimulation.

always clear with 30 μA. Stimulation with intensities >30 μA frequently led to the generation of small contraversive saccades, presumably because of current spread to the extrafoveal regions of the SC motor map. The longest stimulation duration tested was 1,500 ms, and this continued to block occurrence of the saccade.

FIG. 4. Suppression of saccades by unilateral stimulation of the rostral SC. Monkey p performed the visually guided saccade paradigm. Five control trials (---) and 5 stimulation trials (----) are superimposed in each panel. Horizontal bar marks the time of stimulation. Low-frequency, long-duration stimulation (150 Hz, 300 ms, 30 μA) of the left rostral pole delayed leftward (A) saccades longer than rightward (B) saccades. C and D: stimulation of the right rostral pole with the same parameters delayed rightward saccades (D) more than leftward saccades (C).
When we positioned the electrode outside of the location on the motor map where fixation cells were recorded (Munoz and Wurtz 1993), the effect was not evident. When we stimulated at locations above, below, or rostral to where fixation cells were encountered with similar parameters, no effect was seen on saccade generation. Stimulation of the SC caudal to the location of fixation cells elicited small contraversive saccades, presumably because of activation of the saccade-related cells in the extrafoveal SC.

**INTERUPTION OF SACCADeS.** When we applied stimulation to the rostral pole of the SC at the time of movement, saccades were interrupted in midflight. Figure 5 shows examples of saccades that were perturbed in midflight after simultaneous stimulation of both rostral poles in the modified version of the memory-guided saccade paradigm. The fixation point went off at the time of a 50-ms target flash, and the monkey had to look immediately to the location of the flash in complete darkness. Stimulation consisted of a train of either one, two, or four 30-μA pulses at 500 Hz (train duration marked by the vertical dashed lines). The trajectories of the perturbed movements (— — —) deviated from the normal saccades (· · ·) at very short latencies after stimulation (10–15 ms). Note that the severity of the perturbation increased when more stimulation pulses were added to the train; one pulse of stimulation led to only a momentary deceleration in the trajectory of the saccade, whereas four pulses fractionated the saccade into two separate movements. Some of the perturbed saccades were hypometric, a dysmetria that we did not observe when we perturbed visually guided saccades.

The modifications in saccade trajectory illustrated in Fig. 5 followed stimulation given around the time of memory-guided saccade initiation. Figure 6 illustrates the effect of applying stimulation at times before, during, and after the execution of visually guided saccades. Stimulation consisted of a brief, high-frequency train (train of 4 30-μA pulses at 500 Hz) delivered to the left rostral pole. This unilateral stimulation led to interruption of saccades in both rightward and leftward directions. However, with stimulation >40 ms before saccade onset (Fig. 6, top) or within 10 ms of saccade termination (Fig. 6, bottom), the trajectory was not modified. Notice that when saccade trajectory was perturbed, the monkey was able to compensate and reach the target. Similar results were obtained for all directions of saccades.

The perturbations illustrated in Figs. 5 and 6 occurred in
all three monkeys tested with short latencies after stimulation onset. Figure 7 shows the mean latencies from stimulation onset to saccade alteration for each monkey; the mean for all three was 12.9 ms.

In summary, these electrical stimulation experiments show that increased activity of the fixation cells delays the onset of a saccade and interrupts an ongoing saccade. Both of these observations are consistent with the hypothesis that the fixation cells within the rostral SC suppress saccade generation.

GABAergic drugs in the rostral SC

Although electrical stimulation allowed us to increase activity of the fixation cells, injection of GABAergic drugs allowed us to either increase the activity with a GABA antagonist (bicuculline, Fig. 1C) or to decrease activity with a GABA agonist (muscimol, Fig. 1D). We found that bicuculline and muscimol injections into the rostral SC had a profound effect on the monkey's ability to fixate a target and make saccades to a new target. Application of bicuculline increased saccade latencies, whereas muscimol reduced latencies and led to instability of fixation.

Table 1 summarizes the 14 injections that were made in two monkeys. We made a total of six muscimol, five bicuculline, and three saline injections into the rostral pole of the SC where fixation cells had been recorded. The bicuculline injections were fast acting and short lasting, the earliest changes in behavior occurred within 2 min, and with the maximum effect in 7–10 min. After muscimol injection the earliest influences were detected after ~8 min, and the maximum deficit was only revealed at least 30 min after the injection. Bicuculline and muscimol injections also produced side effects that allowed us to monitor the spread of the drugs. After injection of bicuculline, the monkey occasionally generated staircases of three to four small convergent saccades (<2° in amplitude), presumably because of spread of the drug into the extrafusal regions of the SC. The larger muscimol injections usually led to the onset of nystagmus after ~60 min. We attributed this to spread of the drug into the nucleus of the optic tract (NOT), which is located immediately rostral to the SC, because the direction of the slow phase was to the contralateral side. This direction was consistent with the NOT single-cell activity, stimulation, and lesion effects (Mustari and Fuchs 1990; Schiff et al. 1988, 1990). The saline injections produced no observable effects. The modification of saccades we subsequently describe were the maximum observed before the detection of any adverse side effects.

Saccadic reaction times. Figure 8 illustrates the effect of a small bicuculline (Fig. 8, A–C) and muscimol (Fig. 8, D–F) injection into the rostral pole of the right SC of monkey a. Each of the panels (A–F) compares the horizontal eye position traces recorded before (control) and after the injections were made. The injection of bicuculline produced an increase in saccade latency in the visual (Fig. 8A) and memory-guided (Fig. 8, B and C) saccade paradigms.

![Image of a diagram showing saccadic reaction times and latency graphs.](attachment:image.png)
Note that on some trials (e.g., Fig. 8A) the monkey failed to generate the leftward saccade at all. This is similar to the increased latency with electrical stimulation of the rostral SC that we described above (Figs. 2–4).

We observed the opposite effect after the muscimol injection at the same site. Saccades frequently had shorter latencies in both the visual (Fig. 8D) and memory-guided saccade tasks (Fig. 8, E and F). This shortened latency accompanying a presumed decrease in activity of the fixation cells is in contrast to the increased latency with the increased activity after bicuculline injections or electrical stimulation.

Figure 9 quantifies the saccadic reaction times in the visually guided saccade paradigm and shows the latencies for saccades made to targets located 5 and 20° to the left and right of the central fixation point. We pooled the data from all injections into the right rostral pole of monkey a. The vertical dotted lines mark the mean latency obtained in the control condition. The latency to initiate a saccade increased after injection of bicuculline (compare Fig. 9, A and B) and decreased after the injection of muscimol (compare Fig. 9, A and C). These changes, present for both the 5 and 20° saccades, were greater for saccades directed toward stimuli in the hemifield contralateral to the side of the injection (i.e., the leftward saccades) than for saccades to the side ipsilateral to the injection. The saline injections did not significantly affect any of the latency distributions (compare Fig. 9, A and D).

**SUPPRESSION OF SACCADeS.** One of the most striking effects of the muscimol injections was the impairment of the monkey's ability to suppress unwanted saccades. For example, after the muscimol injection illustrated in Fig. 8, E and F, the monkey repeatedly broke fixation after the flash of the target in the memory-guided saccade task and generated the saccade to the target before the appropriate cue (fixation point offset) was given. What is perhaps even more striking is the short latency of these responses (~100 ms) and the subsequent rapid return to fixation and a second saccade to the target that ensued.

This difficulty in maintaining fixation after muscimol injection is indicated by the saccadic reaction times in the memory-guided saccade paradigm (Fig. 10). In this task the peripheral target appeared and was then extinguished, and the monkey was required to delay saccade initiation until after the subsequent offset of the fixation point to receive the reward (correct saccade) (see Fig. 2F of Munoz and Wurtz 1993). If the monkey looked at the target before fixation point offset, the trial was scored as incorrect, and no reward was delivered. We measured saccade latencies from two points: target onset (incorrect saccades) and fixation point offset (correct saccades). Figure 10 shows data for one target position, located contralateral to the side of the injection. In the control situation the monkey was able to delay the saccade to the peripheral target flash until after the offset of the fixation point on all trials (Fig. 10A). The latency distribution was unimodal, centered between 200 and 300 ms. After the muscimol injection (Fig. 10C) the monkey lost much of its ability to suppress a saccade after the target flash in the visual field contralateral to the side of the injection. This effect was not as striking when the target was positioned in the visual field ipsilateral to the side of the injection (not shown). The incorrect responses, generated during the required delay period (i.e., before fixation point offset), moved the eyes to the correct spatial location of the target. The bicuculline and saline injections did not increase the number of incorrect responses. Instead, the bicuculline injection produced an increase in the reaction time for correct responses.

The increase in the number of incorrect saccades after muscimol application also occurred in the overlap saccade paradigm (not shown), when the peripheral target re-
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FIG. 9. Changes in saccadic reaction times in the visually guided saccade paradigm after injection of bicuculline, muscimol, and saline into the right rostral pole of monkey a. Latency histograms are for saccades directed at targets located at 5 and 20° to the left and right. Each histogram shows data from 40 trials with at least 10 trials taken from each injection in the right rostral pole of monkey a. Trials were picked at the time of peak effect but before side effects. Number of trials from a given injection depended on the duration of this optimal period for the given injection. Control samples were taken just before the injection syringe was lowered into the SC. Asterisks denote conditions in which the mean latency differed significantly from control (t test, P < 0.01). Notice that, after muscimol application, saccadic reaction times to leftward targets were reduced, and many responses fell into the range of express saccades. Bicuculline application increased saccade reaction times to leftward targets, whereas saline injections had no effect.

The text describes changes in saccadic reaction times in the visually guided saccade paradigm after injection of bicuculline, muscimol, and saline into the right rostral pole of monkey a. Latency histograms show data from 40 trials with at least 10 trials taken from each injection in the right rostral pole of monkey a. Trials were picked at the time of peak effect but before side effects. Number of trials from a given injection depended on the duration of this optimal period for the given injection. Control samples were taken just before the injection syringe was lowered into the SC. Asterisks denote conditions in which the mean latency differed significantly from control (t test, P < 0.01). Notice that, after muscimol application, saccadic reaction times to leftward targets were reduced, and many responses fell into the range of express saccades. Bicuculline application increased saccade reaction times to leftward targets, whereas saline injections had no effect.

In this task the monkey also generated more incorrect saccades when the target appeared in the visual field contralateral to the side of the injection, and many of the incorrect responses were generated after extremely short reaction times. Injection of bicuculline or saline did not increase the number of incorrect responses, but the bicuculline application did produce an increase in latency for correct responses.

Express Saccades. Note that, in the control and saline conditions in the visually guided saccade task (Fig. 9, A and D), most responses fell into a unimodal distribution; for 20° leftward saccades, for example, this was centered at ~300 ms. Application of muscimol produced a bimodal distribution of latencies for leftward saccades with the first peak occurring between 100 and 150 ms after the target onset (Fig. 9C). These short-latency responses are reminiscent of the express saccades that are elicited at latencies of ~100 ms or less after target onset (Fischer and Boch 1983). The emergence of saccades with short latencies after muscimol injections was even clearer in the memory-guided saccade paradigm (Fig. 10C), in which many of the incorrect saccades were elicited <150 ms after onset of the target flash.

To explore further the relation of the fixation cells to the frequency of express saccades, we also had the monkey generate saccades in the gap saccade paradigm (see Fig. 2H of Munoz and Wurtz 1993) because express saccades are prevalent in this task. In the control condition (Fig. 11A) the peak in the latency histogram was at ~110 ms for leftward saccades. This latency peak was only slightly shorter after muscimol injection (Fig. 11C), because presumably there was a lower latency limit that already had been approached in the control conditions. Application of bicuculline elimi-
cantly after muscimol injection. After the saline injection, there was no statistical difference in the percentage of saccades having latencies <100 ms in any experiment.

Thus reduction of fixation cell activity after muscimol injection led to a clear increase in the frequency of saccades occurring at or near the short-latency characteristic of express saccades, whereas bicuculline application eliminated these responses.

**FREQUENCY OF SPONTANEOUS SACCADES.** The injection of muscimol and bicuculline into the fixation zone also modified the frequency of spontaneous saccades made by the monkey in the intertrial intervals. During this period the monkey faced the diffusely lit tangent screen that covered 70° x 70° of the central visual field. For each condition (control, muscimol, bicuculline, saline) we analyzed 100 intertrial intervals, consisting of the 1.75 s before each new trial started. Figure 13A compares the average frequency of

![Graph showing the frequency of saccades](image)

**FIG. 10.** Test of the monkey's ability to suppress saccades in the memory-guided saccade paradigm after injection of bicuculline, muscimol, and saline. Saccades elicited immediately after target onset were scored as incorrect, and those evoked after fixation point offset were scored correct. Latency histograms are shown for incorrect and correct saccades made to targets at 20' to the left of central fixation. Asterisks denote conditions in which mean latency differed significantly from control (t test, P < 0.01). Same injections and selection of trials as in Fig. 9. Note the striking increase in the number of incorrect responses triggered after extremely short reaction times after muscimol application. This decrease in the percentage of correct responses was highly significant (χ², P < 0.01).

nated this peak and produced longer latencies (Fig. 11B). Once again the saline injection had no effect (Fig. 11D).

If we define saccadic latencies of <100 ms as being express saccades, we can compare the frequency of express saccades before and after the injection of the GABAergic drugs. Figure 12 shows the percentage of trials in which saccadic reaction times to targets in the contralateral field in the gap paradigm were <100 ms for the two monkeys tested. *Monkey g* (Fig. 12A) rarely made express saccades to the 20° target in the control situation, but this percentage increased dramatically after the application of muscimol. *Monkey a* generated express saccades to the 20° (Fig. 12B) and 5° (Fig. 12C) targets 10% and 24% of the trials, respectively, in the control condition. These percentages dropped significantly after bicuculline injection and increased signifi-

**FIG. 11.** Changes in saccadic reaction times in the gap saccade paradigm after injections of bicuculline, muscimol, and saline. Latency histograms are shown for saccades directed at targets located 20° to the left. Same injections and selection of trials as in Fig. 9. Asterisks denote conditions in which the mean latency differed significantly from control (t test, P < 0.01). Notice that the monkey made many express saccades in the control, muscimol, and saline conditions but none after application of bicuculline.
saccades in these control conditions. The monkey averaged 2.1 saccades/s in the control situation. After injection of muscimol, this increased to 3.1 saccades/s (t test, P < 0.0005) and decreased after bicuculline application to 1.3 saccades/s (t test, P < 0.0005). There was no significant change in the frequency of spontaneous saccades after the injection of saline.

We also determined the duration of each period of fixation under the same four condition. Figure 13C shows the mean duration of fixation, and Fig. 13C shows the variation of all fixation durations for the four conditions. In the control condition the average period of fixation was 397 ms. This period dropped to 241 ms after muscimol application, increased to 364 ms after bicuculline, and dropped to 343 ms after saline injection. These changes were all significant (t test, P < 0.005). Note that the distribution of fixation durations in all conditions were unimodal with a peak around 200 ms (Fig. 13C). The duration ranged from 100 to >1,600 ms. The presence of muscimol eliminated almost all fixations beyond 400 ms (thereby increasing the number of observations), whereas the presence of bicuculline increased the number of long-duration fixations (thereby reducing the number of observations). The only major difference between the control and saline distributions was the paucity of long-duration (>1,000 ms) fixations in the saline condition. This presumably led to the difference in mean fixation periods between the two conditions (Fig. 13B).

**Saccade Dynamics.** The unilateral injections of muscimol and bicuculline also affected saccadic trajectories. These effects were most striking for saccades directed contralateral to the side of the injection. Figure 14 shows the effects of muscimol (−−) and bicuculline (−−−) compared with the trajectory of normal saccades (dotted traces) under visually guided and memory-guided saccades in two monkeys. Figure 14A shows, for monkey g, that the average position and velocity trajectories (averaged from 20 saccades, aligned on saccade onset) for saccades to targets 20° contralateral to the side of the injection were faster and had shorter durations after injection of muscimol. Injection of bicuculline led to slower saccades with longer durations. These injections also produced a small amount of dysmetria; muscimol injection led to hypermetria, whereas bicuculline produced a hypometria.

Saccade trajectories were less affected in monkey a in which smaller injections were made into the right rostral pole (see Table 1). Figure 14, B and C, shows the average position and velocity traces (averaged from 10 saccades, aligned on saccade onset) for saccades that were 20° and 5° to the left, respectively. After injection of muscimol, the 20° saccades were faster and had shorter durations, but the speed and duration of the 5° saccades were not affected. Bicuculline injection also had only a subtle effect, slowing the memory-guided saccades more so than the visually guided saccades. Saline injection (not shown) did not significantly affect the trajectories of either the 5° or 20° saccades. Note also that the injections in monkey a (Fig. 14, B and C) did not produce any noticeable dysmetria. In net, although the velocity and duration of visually guided and memory-guided saccades were affected, the amplitude was less affected, if at all.

**Discussion.**

We tested the hypothesis that fixation cells in the rostral pole of the monkey SC controls the generation of saccades. We altered the activity of fixation cells with electrical stimulation and injection of GABAergic drugs. Increasing activity by electrical stimulation or the GABA blocker bicuculline delayed the onset of saccades. Decreasing activity by the GABA agonist muscimol led to a reduction in saccade latency and difficulty in maintaining fixation. Both directions of change are consistent with the hypothesis that activation of fixation-related cells in the rostral SC is necessary to maintain visual fixation, whereas a pause in the discharge of these cells is a prerequisite for the initiation of a saccade. These results support this hypothesis and indicate how the SC fixation cells fit into the oculomotor system.
Relation of the fixation cells to the oculomotor system

We conclude from these experiments that modulation of the fixation cells results in a change in the frequency of saccades. Increasing the activity of the fixation cells held off the generation of saccades, and reducing activity led to earlier saccade generation. This is consistent with our hypothesis (Fig. 15) that the fixation cells (FTX) in the rostral SC inhibit (either directly or indirectly via interneurons) the saccade-related cells (SAC) in the more caudal SC or in the brain stem. Figure 15 also emphasizes the push-pull nature of the interaction between the fixation cells and saccade cells, which, although logically hypothesized on the basis of single-cell recording (Munoz and Guitton 1989, 1991; Munoz and Wurtz 1993), can be seen more clearly with the type of experimental manipulations used in this study.

When the effects of the present bicuculline and muscimol injections in the rostral pole of the SC are compared with those observed previously in the saccade regions of the SC (Hikosaka and Wurtz 1985), a striking push-pull interaction is apparent. We found that the presumed reduction of activity of the fixation cells after muscimol injection was followed by a difficulty in maintaining fixation as evidenced by both the increased frequency of express saccades and a breaking of fixation and return to the original fixation position again (e.g., see Fig. 8E). This break and return of fixation is similar to the square wave jerks seen after the presumed increase in activity in the saccade part of the SC after the injection of bicuculline (Hikosaka and Wurtz 1985). Conversely, the delay of saccades after injection of bicuculline in the rostral pole is similar to the delay observed after decreased activity with a muscimol injection in the saccade region of the SC (Hikosaka and Wurtz 1985). These observations suggest that the generation of a saccade results from the balance of activity between the fixation and saccade cells of the SC. Whether a saccade occurs depends on the relative activity in both regions. Even after the saccade starts, the alteration of saccade dynamics produced by electrical stimulation of the rostral pole presumably also results from a change in the balance between the fixation and saccade cells. We assume such a balance may also exist between the fixation cells and other saccade-related cells in the midbrain and pons.

The unilateral electrical stimulation and drug injections influenced saccades related to the contralateral as well as the ipsilateral SC. This indicates that there may be interactions between the colliculi on the two sides of the brain. Injection of muscimol or bicuculline into one rostral pole produced a greater effect on contraversive saccades. In so
FIG. 14. Modification of saccade dynamics by injection of muscimol (---) and bicuculline (- - - ). Control trajectories are dotted. Saccade trajectory is shown for visually guided and memory-guided saccades. A: injections made into the left rostral pole of monkey A with the target located 20° right. The position (Eh) and velocity traces (Eh) were averaged over 20 trials and aligned on saccade onset. B and C: injections made into the right rostral pole of monkey A with saccades made to targets located 20 ° down (D) or 5° (C) left. Traces were aligned on saccade onset and averaged over 10 trials.

far as saccade generation is dependent on the SC, these results demonstrate again the importance of the presumed inhibition between the fixation and saccade cells within the same SC (Fig. 15).

In contrast to the effects of the GABAergic drugs, unilateral electrical stimulation of the rostral pole sometimes affected ipsiversive saccades more than contraversive saccades. Saccades related to the SC contralateral to the side of stimulation (i.e., those made to stimuli in the visual field on the same side as the SC stimulated) were the most clearly delayed in onset (see Fig. 4, A and D). Those saccades related to the same colliculus stimulated (i.e., those to the opposite visual field) were not always fully blocked and were hypometric when they occurred (see Fig. 4, B and C). This was opposite to the effect produced by the bicuculline injection, which also presumably led to increased activation of fixation cells.

If this asymmetry is related to interactions within the SC, our interpretation is based on the likelihood of the electrical stimulation affecting not only the fixation cells lying adjacently to the stimulating electrode but the fibers to and from the opposite SC as well. Some preliminary results show that stimulation of one rostral pole leads to orthodromic and/or antidromic activation of at least some fixation cells in the opposite rostral pole (Munoz et al. 1993). The orthodromic activation occurred at monosynaptic latencies (<1.5 ms). These postulated excitatory commissural connections are shown in Fig. 15. In the cat it was shown that synaptic terminals arising from the contralateral SC were excitatory as well as inhibitory (Belan 1985) so that an anatomic substrate for the excitatory connections postulated in Fig. 15 does exist. The transfer of excitation from fixation cells on one side to cells on the opposite side would make it possible for fixation cells on one side to influence saccade-related cells in the contralateral as well as the ipsilateral colliculus. Indeed, we have found that saccade-related cells in the caudal SC are inhibited at very short latencies (<2 ms) by stimulation of either rostral pole (Waltzman et al. 1990; Munoz et al. 1993). Electrical stimulation of one rostral pole would lead to both orthodromic and antidromic activation of fixation cells on the opposite side, while the unilateral bicuculline injections would only produce some orthodromic activation of fixation cells on the opposite side. This may account for the differences observed between the bicuculline injections and the unilateral electrical stimulation on modulation of ipsiversive and contraversive saccades.

Relation of the fixation cells to express saccades

One of the most striking effects produced by the muscimol injections was the onset of many short-latency saccades that were similar to the express saccades made by normal monkeys (Fischer and Boch 1983). In a series of experiments, Fischer and his collaborators showed that the frequency of these saccades was influenced by the intensity, size, and location of the stimulus (Boch et al. 1984), and the extent of training and the type of behavioral paradigm used (Fischer et al. 1984). We think it is legitimate to compare the short-latency saccades after muscimol injection to those express saccades.
express saccades because our artificially induced short-latency saccades meet the key criterion for identifying express saccades: a bimodal latency distribution with the first peak in the histogram of saccadic latencies at <100 ms (Boch and Fischer 1986). The peak in the latency histogram described by Fischer and Boch (1983) occurred at ~70-80 ms when target location was predictable. In our experiments the target was randomly presented either to the left or right of the fixation point, and such randomized presentation has been shown to increase the peak latency of the histogram in humans (Fischer and Ramspurger 1986).

Fischer and his collaborators developed the hypothesis that express saccades occurred in cases when the subject had been released from active visual fixation before target onset. In the gap task this corresponds to the predictable removal of the fixation point. In our experiments we think that the removal of the SC fixation cells with muscimol accomplishes the same break of fixation. Furthermore, our experiments indicate that an intact rostral SC is necessary for the reduction in the frequency of express saccades.

The effect of altering the fixation cell on the frequency of express saccades also gives an indication of the relative role of the rostral SC in a possible fixation system within the brain. If the fixation cells acted on all parts of the saccadic system throughout the brain, elimination of the SC should release these zones from inhibition and increase the number of express saccades. Instead, ablation of the entire colliculus eliminates express saccades while sparing longer latency saccades (Schiller et al. 1987). This is in contrast to the observation that ablation of the frontal eye fields does not eliminate either normal or express saccades (Schiller et al. 1987). That other brain areas act on fixation cells is suggested by the increased frequency of express saccades after ibotenic acid lesions of area V4 of extrastriate cortex (Weber and Fischer 1990). From what we now know, a decrease in the activity of the fixation cells appears to be necessary for the generation of express saccades, because the presence or absence of activity in this area can block or release the expression of these saccades.

The relation of the SC fixation and saccade cells to express saccades is also suggested by the recent observation of a dead zone in the central 2° for express saccades (Weber et al. 1992). That is, both humans and monkeys cannot make express saccades to targets located within the central 2° of the visual field, in contrast to the lack of such a zone for longer latency saccades (Wymann and Steinman 1973). One explanation for this difference is based on the saccade-related discharges of fixation cells. If we assume that the absence of fixation cell activity in both rostral pole is a prerequisite for the generation of express saccades, then, because some fixation cells do not pause for small contraversive saccades (see Fig. 11 of Munoz and Wurtz 1993), some fixation cells would always be somewhat activated by small saccades. If we assume that normal latency saccades can occur in spite of some fixation cells being active, these longer latency saccades would continue to occur.

Relation of the fixation cells to attention and motor control

Several discussions of the mechanisms underlying shifts of visual attention even in the absence of overt eye movements have also invoked the idea of a fixation system. For example, Nosey and his collaborators (Nosey et al. 1984; Rafal et al. 1988) have suggested that a covert shift of attention involves first a disengagement from the previous location of visual attention, then a movement of that attention, and then engagement of the attention at the new location. A possible neural mechanism for the engagement and disengagement of attention might be a modulation of activity of the fixation cells in the rostral pole of the SC, but we have no direct evidence on this point.

The recognition of a fixation system in oculomotor control allows us to contribute to an understanding of motor control in general. Inhibition of movement can result from activity of a specific functional system within the brain, not the disruption of the motor system. The push-pull interaction that we have described between the fixation and the saccade system may very well exist in other motor systems as well.

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