

Saccadic eye movements following injection of lidocaine into the superior colliculus

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Summary. Ablation of the superior colliculus (SC) has generally produced limited deficits in the initiation of saccadic eye movements, usually an increase in the latency of saccades. However, recent studies using muscimol, a GABA agonist, to block afferents to the SC showed deficits in not only latency but in amplitude and velocity of saccades as well. These greater deficits might be dependent upon the testing of saccades shortly after the damage of SC before any compensation for the deficits could develop. The present experiments tested this hypothesis by injecting a local anesthetic into SC. The anesthetic inactivated the cells entirely rather than just deafferenting them, but still allowed testing immediately after the injection. Clear deficits were observed following injection of lidocaine into the SC. The amplitudes of saccades to visual targets were shortened, and the peak velocities of the saccades were reduced even if the reduced amplitude of the saccades was taken into account. Latency of saccades usually increased. The deficits were limited to the area of the visual field that overlapped the movement fields of the cells near the injection site. If the movement fields were in the periphery, saccades to the periphery were shortened following the injection of lidocaine. If the movement fields were near the center of gaze, saccades into the area were shortened, but the monkey was able to make saccades over the visual field related to the affected area to more peripheral targets. These experiments support the view that the SC normally conveys information on the amplitude and velocity of saccadic eye movements, but that gradual compensation can be made over time by other pathways when damage to the structure occurs.

Key words: Superior colliculus - Saccades - Eye movements - Behaving monkey - Lidocaine injection - Reversible lesion

Introduction

The superior colliculus (SC) of the primate plays a key role in the initiation of saccadic eye movements. Cells in the intermediate layers discharge before saccades, with the discharge of each cell related to a particular range of saccadic directions and amplitudes (Schiller and Koerner 1971; Wurtz and Goldberg 1972a; Sparks et al. 1976; for review see Wurtz and Albano 1980). These cells are organized within the intermediate layers of SC so that their movement fields form a topographic map, primarily of the contralateral visual field. Cells in these intermediate and deeper layers project to the contralateral ponto-medullary reticular formation (Harting 1977) and have excitatory connections with burst neurons (Hikosaka and Kawakami 1977; Raybourn and Keller 1977). Electrical stimulation in intermediate and deep layers elicits saccadic eye movements towards the area where adjacent cells have their movement fields (Schiller and Stryker 1972; Robinson 1972).

Ablation of the primate SC, however, has produced surprisingly mild deficits in saccadic eye movements (Wurtz and Goldberg 1972b; Mohler and Wurtz 1977; Schiller et al. 1980; Albano and Wurtz 1982). An increase in latency of saccades (Wurtz and Goldberg 1972b; Mohler and Wurtz 1977; Albano et al. 1982), some change in their velocity (Wurtz and Goldberg 1972b; Schiller et al. 1980), and a shortening of saccades as indicated by an increase in the number of corrective saccades (Mohler and Wurtz 1977) have been reported. However, in a recent

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study (Hikosaka and Wurtz 1985), we did not ablate the SC, but instead interfered with the afferents to SC, and were able to show much more dramatic deficits. Application of muscimol, a GABA agonist that should increase tonic inhibition of SC cells and functionally deafferent them, produced the expected longer latency but also a decrease in velocity and amplitude of saccades. The deficit in saccadic accuracy was less with saccades to visual targets that were present as opposed to remembered visual targets.

We suggested that the relative lack of deficit for saccades in previous studies was related to compensation by the monkey for the collicular damage (Hikosaka and Wurtz 1985). Saccadic eye movements were studied within minutes of injection of muscimol into SC, presumably too soon for compensation to occur. In contrast, test following ablation of SC had been made a day or frequently a week after the ablation had been made, and this delay might have allowed time for compensation for the deficit. What had then been studied was the compensation for the deficit not the deficit itself.

The limitation to our interpretation is that in our experiments the SC cells were not removed, only their inputs were altered. An indication of this was the continued low threshold stimulation current required to elicit saccades during the maximal effects of muscimol. An alternative method would be the use of a local anesthetic to inactivate SC cells such as has been effectively done in the study of transmission in the lateral geniculate nucleus (Malpeli et al. 1981) and in the analysis of the olivocerebellar system in relation to vestibuloocular reflex plasticity (Demer and Robinson 1982).

In the present study we examined the effects of a localized, functional removal of the SC by injecting a local anesthetic, lidocaine, into the SC. By recording and stimulating through the injection pipette, we were able to determine the area of the visual field related to the injection site. By examining saccades before and just after injecting lidocaine, we were able to see the immediate effects of localized inactivation of the SC. We have found that such injections produce clear deficits in the amplitude and velocity of saccades.

Methods

The methods used in training the monkeys, locating and injecting specific regions in the SC, and analyzing any resulting deficits in saccadic eye movements have been described in detail previously (Hikosaka and Wurtz 1985). The procedures used in the present experiments are identical to those in this previous report and only a brief summary of these methods is presented here.

We trained the monkeys to look at a spot of light (the fixation point) and to detect a dimming of it in order to obtain a liquid

reward. When this fixation point went out and another spot of light (the saccade target) came on, the monkey was trained to make a saccade to that second spot of light. The location of the saccade target was randomly determined on any given trial. We measured the latency, amplitude, and peak velocity of the saccades and compared these parameters before and after the injection of lidocaine.

Monkeys were prepared for single cell recording from the SC under general anesthesia (pentobarbital sodium). Following surgery monkeys were given an analgesic for several days and allowed to recover for at least a week before water intake was controlled. During the training and experiments, the monkey's weight was checked each day, and added fruit or water was provided as needed.

We inserted an injection pipette into the SC while monitoring neural activity recorded by a tungsten microelectrode fitted into the injection pipette. We identified the intermediate layers of the SC by the burst of activity that preceded saccades. This location within the intermediate layers, was later confirmed by locating micro-lesions made at injection sites on subsequently obtained histological sections. Stimulation at the site was also used to verify the area of the visual field to which the SC region was related. A 2% solution of Xylocaine (lidocaine hydrochloride) was pressure injected through the pipette into the SC. Volumes ranged between 1 and 5 μ l.

Results

We made 5 injections of lidocaine into the intermediate layers of the SC in two monkeys. All injections modified saccades in similar ways. We will use two cases to illustrate these effects, one in the peripheral field, and one near the center of gaze.

Figures 1-5 show the results of an injection of lidocaine into the left SC and its effect on saccades made to peripheral targets in the right visual field. We determined the area of the visual field related to the SC region around the tip of the pipette by recording single cell activity and by electrical stimulation. Right-downward saccades were evoked by stimulation with a train of pulses through the electrode (Fig. 1A). Amplitudes of the stimulus-evoked saccades depended on whether or not the monkey was looking at the fixation spot. If the stimulation was delivered while the monkey was fixating in order to detect the dimming of the fixation point (Fig. 1A, left), the stimulus-evoked saccades were counteracted by eye movements that redirected the eye back to the fixation point. If the stimulation was delivered while the monkey was not fixating (Fig. 1A, right), a saccade of greater and more variable amplitude was evoked. This confirms the previous report of Sparks and Mays (1983) that saccades evoked by SC stimulation during fixation are shorter than those evoked during random fixations.

Figure 1B shows saccades made to the area of the lower right visual field that was related to cells at the injection site. Following an injection of 8 μ g of

lidocaine in 1.6 μ l of saline, there was a decrease in neural activity recorded through the microelectrode within a few seconds. Electrical stimulation after the injection was complete failed to elicit any eye movement even when we raised the stimulus currents from 15 μ A up to 160 μ A.

Effects on saccades to visual targets were present as soon as the saccades were measured after the injection: effects were evident 2 min after the injection and the electrode was removed within 15 min to avoid any further discharge of lidocaine from the pipette. Figure 1C shows saccades obtained 20 min after the injection. In contrast to the saccades made before the injection (Fig. 1B) which reached points close to the visual targets (10°, 20°, and 30° eccentricity) with only small corrective saccades, saccades after the injection (Fig. 1C) fell short of the targets. This was particularly evident for saccades to more eccentric targets. The subsequent corrective saccades also fell short of the targets. Consequently, the monkey made three saccades before his eye was centered on the target. The velocities of the saccades were lower but latency remained largely unchanged.

These changes in saccades were limited to right downward saccades, those directed toward the visual field related to the region of SC injected. This is illustrated in Fig. 2 which shows the trajectories of the saccades. Figure 2A shows the saccades evoked by stimulation during fixation; these are the same records as in Fig. 1A, left. Figure 2B shows trajectories of two saccades made to targets at an eccentricity of 20° for 10 directions before the injection. Only the first saccades made after onset of the visual target are shown. Within 20 min after the injection (Fig. 2C), saccades to the two targets in the lower right quadrant clearly became shorter whereas the other saccades remained unchanged. The saccades were consistent across trials: the two saccades to each

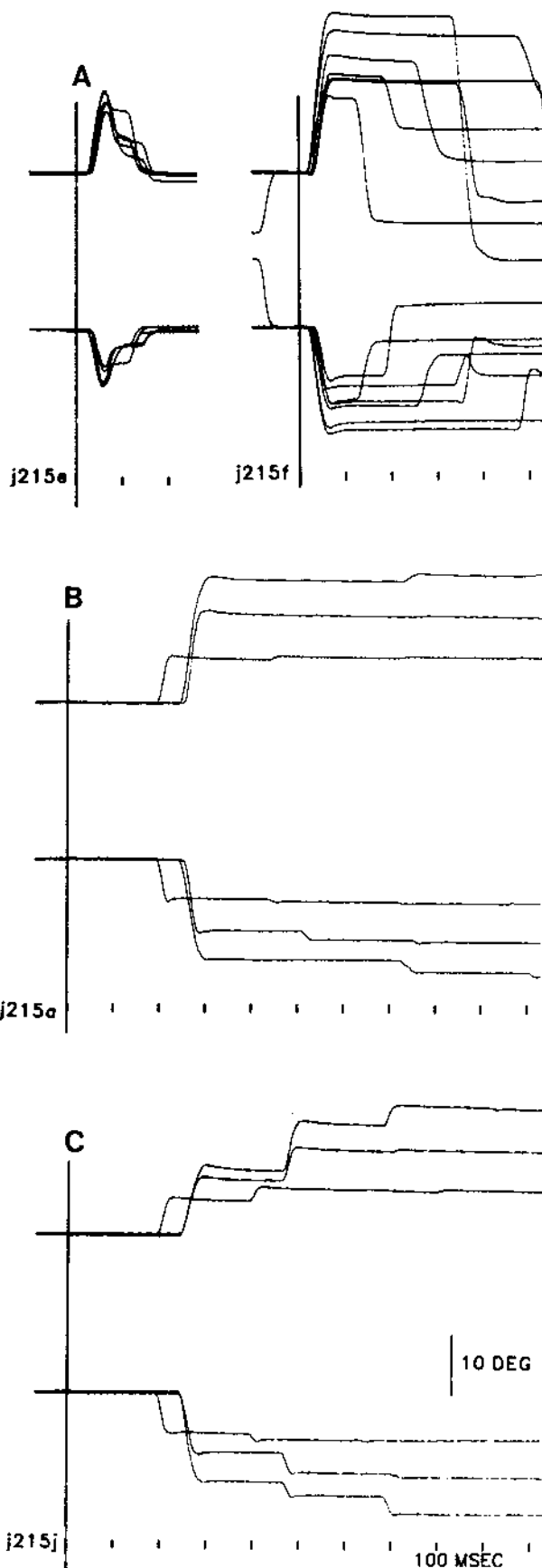
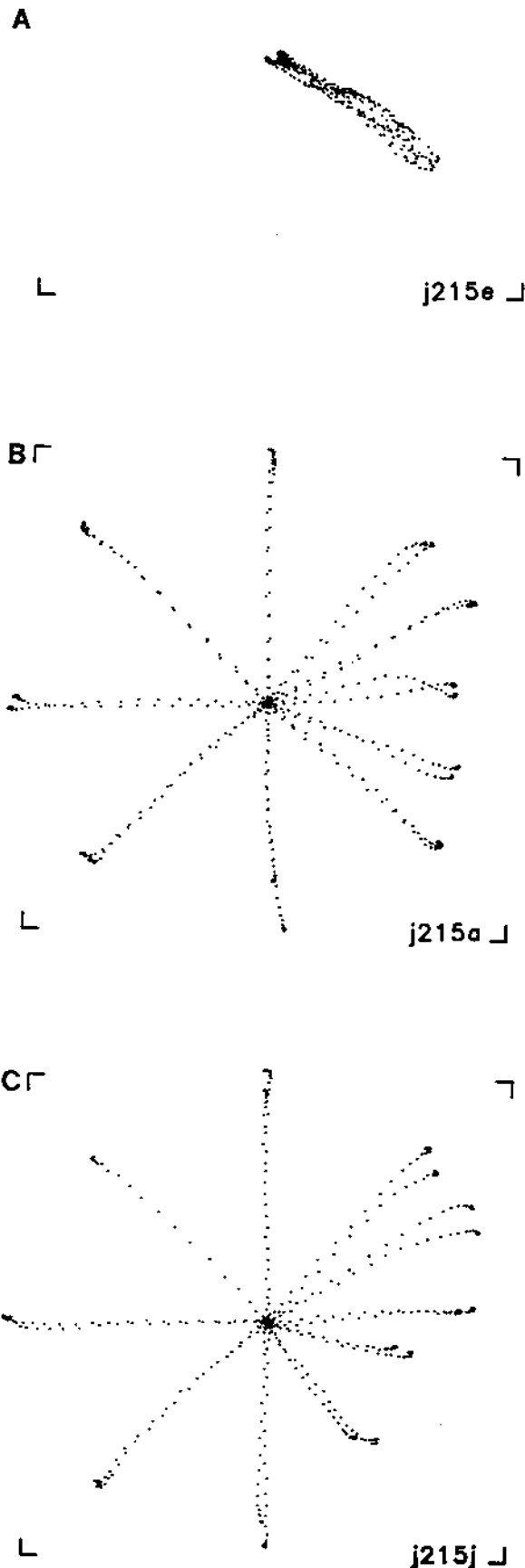


Fig. 1A-C. Shortening of saccades after an injection of lidocaine in the left SC. Upper traces show horizontal eye positions (right is upward, left downward); lower traces show vertical eye positions (up is upward, down downward). A saccades evoked by electrical stimulation at the injection site before the injection. Threshold was 15 μ A for a train of biphasic negative-positive pulses (200 Hz, 50 ms) with each pulse 0.2 ms. On the left stimulation was delivered while the monkey was fixating a spot of light. On the right stimulation was delivered while the monkey was not fixating; eye position was aligned as if the saccades started from the same position. Vertical line indicates the onset of stimulation. B and C superimposed traces of saccades which the monkey made to visual targets before (B) and 20 min after (C) the injection. Target positions were to the right and 45° downward with eccentricities of 10°, 20° and 30°. Vertical line indicates the onset of the target. Lidocaine injected was 8 μ g in 1.6 μ l of saline solution. Results of the same injection are also shown in Figs. 2-5



target had nearly identical trajectories both before and after the injection, they were just shorter after the injection. The right-downward direction was exactly the direction of the stimulus-evoked saccades (Fig. 2A). This correspondence was seen following every lidocaine injection, and suggests that the shortening of saccades resulted from a localized dysfunction of SC cells near the injection site.

Figure 3 provides more quantitative evidence for this localized effect within the SC. The map of cell discharge (Fig. 3, Cell discharge) shows the difference in discharge before and after the onset of the saccade target and indicates the location of the movement fields of cells at the site of the injection. Only large saccades to targets in the lower right quadrant were preceded by increased cell discharge. The rest of Fig. 3 shows the difference in measures of saccadic parameters before and after the injection. Substantial decrease in saccade amplitude (Fig. 3, Saccade amplitude) occurs at 4 points at 20° and 30° eccentricity in the lower right quadrant with little change seen for saccades to the other targets. The distribution of saccades with reduced amplitude is remarkably similar to those for changes in cell discharge.

Changes in the latencies of saccades to the affected part of the visual field were not evident in this monkey (Fig. 3, Latency of saccade). Increase in saccade latency did occur however, in the other monkey that was less well trained: the increase was between 100–300 ms for points in the affected area.

Peak velocities decreased for saccades to targets in the same lower-right quadrant area (Fig. 3, Peak saccadic velocity), but, these changes may not be significant since the amplitudes of saccades made to these points decreased so that lower velocities would be expected. Therefore, we plotted peak velocities of saccades to the affected area as a function of the amplitude of the saccade actually made (Fig. 4). This comparison of peak velocity before (filled circles) and after (open squares) the lidocaine injection shows that the peak velocities were lower after the injection particularly for longer saccades. The peak

Fig. 2A-C. Changes in trajectories of saccades following the injection of lidocaine into the left SC. A saccades evoked by electrical stimulation while the monkey was fixating the center of the screen. B and C saccades made by the monkey to visual targets before (B) and 20 min after (C) the injection. Eye positions are displayed only for the period from the offset of the fixation point to the end of the first saccade. Target eccentricity was 20° in each direction. Length of each side of the square (distance between two angles of the square) is 40°. Trajectories of 2 saccades are superimposed for each target. Time interval between dots was 2 ms. Note shortening of saccades to the lower right quadrant

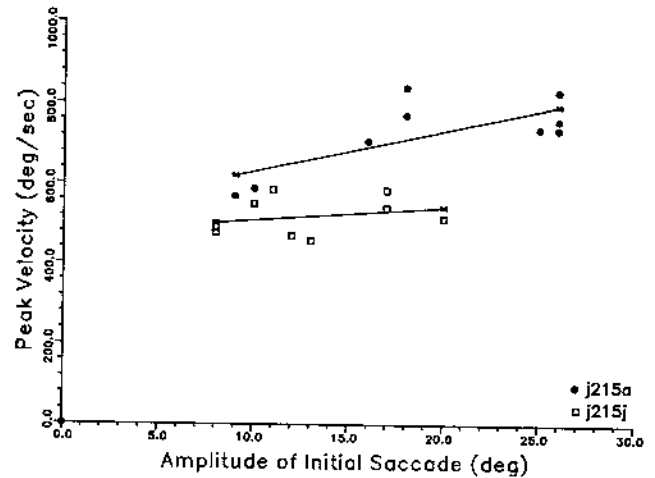
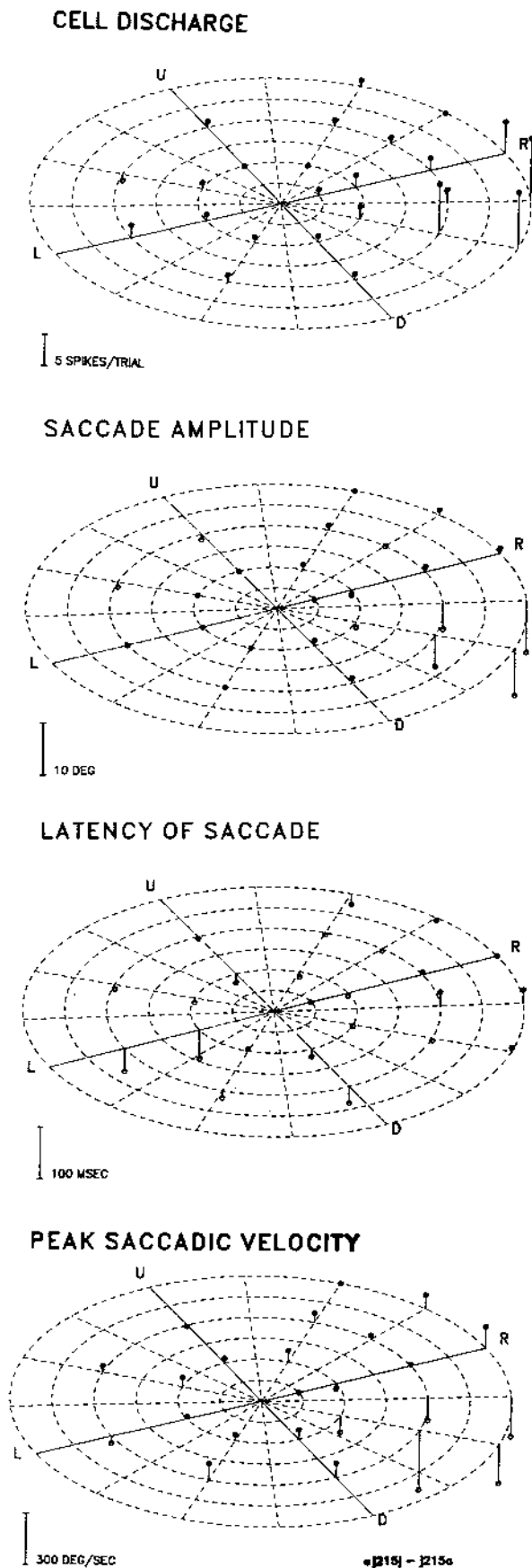


Fig. 4. Peak velocity of saccades before (filled circles) and 20 min after (open squares) the lidocaine injection. Amplitudes of saccades to 5 visual targets in the lower right quadrant that were maximally affected by the injection (see Fig. 3) are plotted against peak velocities. After the injection, the velocity decreased particularly for longer saccades

velocities after the injection showed little increase with increased saccadic amplitude.

The deficits in saccades to visual targets did not increase further beyond that seen 20 min after the injection. We observed substantial recovery 1 h after the injection and almost complete recovery after 2 h 30 min. This time course was paralleled by recovery of threshold for stimulus-evoked saccades. In one of the other injection experiments we left the pipette in the SC and tested the threshold throughout the recovery period. Before the injection the threshold was 15 μ A. It went up to more than 150 μ A within 2 min of the injection, but gradually decreased to 130 μ A within 20 min, 58 μ A after 34 min, 40 μ A

Fig. 3. Localized area of the visual field affected by lidocaine injection. Each parameter is plotted on the basis of target positions. Cell discharge shows that saccade-related neural activity at the injection site is largely limited to the periphery beyond 20° eccentricity in a part of the lower right quadrant of the visual field. Spikes were recorded as multi-unit activity just before the injection and the figure shows the difference in discharge at each point for the 300 ms before and after target onset. The discharge is primarily related to movement but also incorporates any slight visual response as well. For Latency of saccade, Peak saccadic velocity, and Saccade amplitude, the value at each point shows the difference in each parameter before and after the injection. Increase is plotted upward, decrease downward. Decrease in peak velocity and amplitude of saccades corresponds to the cell's movement field shown in Cell discharge. Every data point in all segments of the figure is the average of two trials. Eccentricities of dashed circles are 5°, 10°, 15°, 20°, 25°, and 30°. R, L, U, D indicates right, left, up, and down

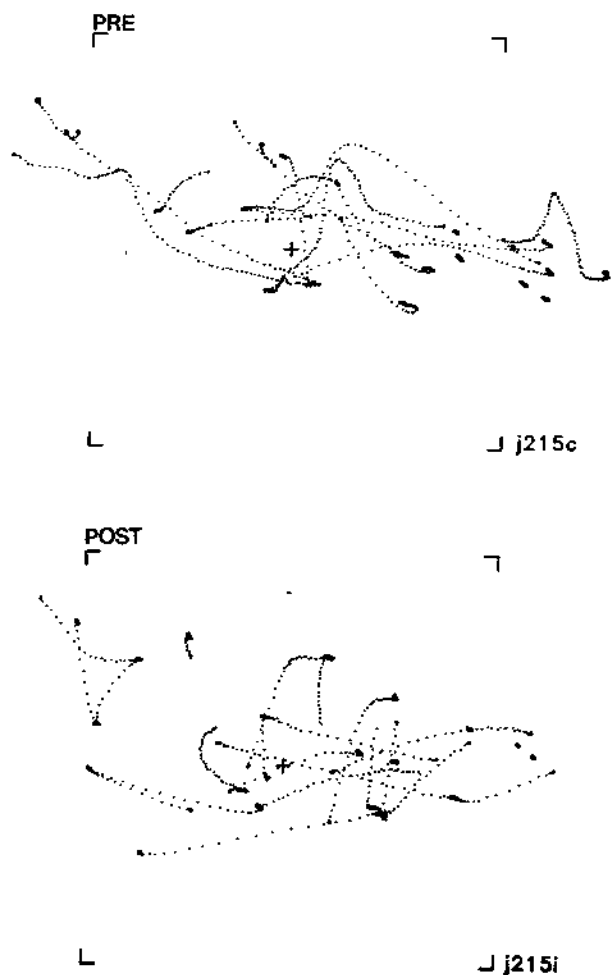


Fig. 5. Lack of effect of lidocaine injection on spontaneous eye movements. Trajectories obtained in a period of 10 s are shown before (Pre) and 14 min after (Post) an injection of lidocaine in the left SC. The experimental room was dimly lit throughout the recording. Each display is composed of a series of 10 discontinuous records each of which is 1 s long. A small cross at the center indicates the approximate center of the orbit. Same organization as in Fig. 2

after 51 min, 37 μ A after 68 min, and 27 μ A after 136 min.

With the doses of lidocaine we used, no apparent change in spontaneous eye movement was observed (Fig. 5). The direction of gaze was largely confined to the central 40° before the injection (Fig. 5, Pre) as well as after the injection (Fig. 5, Post). The frequency, direction, and velocity of saccades showed no qualitatively obvious changes.

The decrease in amplitude and velocity of saccades to the peripheral targets might suggest that lidocaine injected into the SC merely decreases the output of the SC to the brainstem oculomotor system and thus reduces the velocity and amplitude of large saccades. Saccades shown in Fig. 6, for a lidocaine

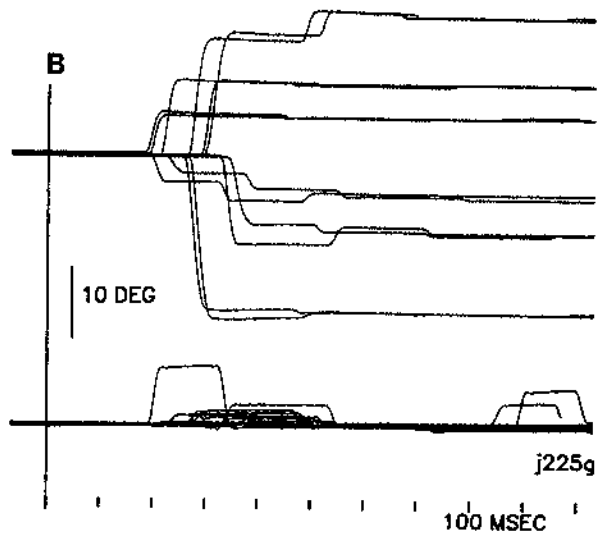
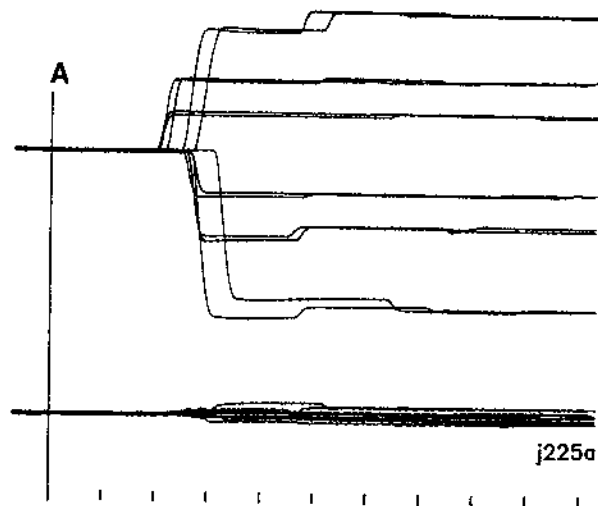
injection made close to the representation of the fovea within SC, reject this hypothesis. In this case the injection was made into the right SC, and electrical stimulation indicated that the region injected was within 5° of the fovea in the left visual field. Figures 6A and 6B show saccades to points 5°, 10°, and 20° to the right and left before (Fig. 6A) and 5 min after (Fig. 6B) the injection. The amplitude was clearly decreased for saccades made to the contralateral target with an eccentricity of 5°, but not for those made to 10° and 20° targets. On the other hand, the latency was increased most clearly for saccades to the contralateral 10° target instead of the 5° target while the latency for saccades to the target 20° on the left was unaffected.

This experiment demonstrates that the monkey could "saccade over" an area of the visual field affected by the injection. This same point can be seen in Fig. 6C which shows the change in saccade amplitude throughout the visual field before and after the injection. While the maximum extent of the deficit extended as far out as 15° on the horizontal meridian on the left, the monkey was able to saccade over this part of the field to the 20° target with no deficit.

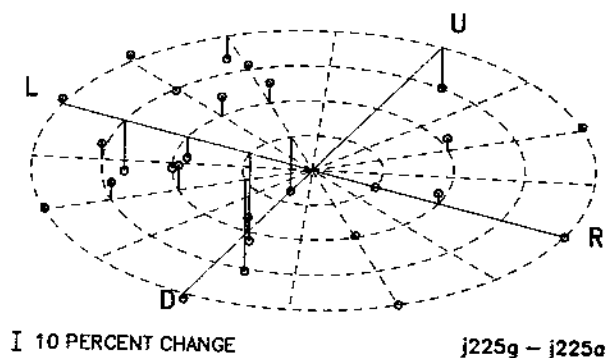
Discussion

Local anesthetics such as lidocaine are thought to permeate the nerve cell membrane and block ion channels from inside the membrane, eliminating generation or conduction of action potentials (Ritchie 1979). If the concentration of the anesthesia is high enough in the SC, impulse conduction is blocked, at least at the proximal axons of the output cells, and this should produce effects equivalent to the ablation of these cells. We found that electrical stimulation at the site of the lidocaine injection in SC, even with elevated stimulation currents, no longer produced saccades after the injection, and this is consistent with the expected action of the local anesthetic.

This inactivation of cells by lidocaine is different from the action of muscimol, a GABA agonist, which we used in a previous study (Hikosaka and Wurtz 1985). Muscimol hyperpolarizes the cell membrane as it increases its conductance while sparing the cell's ability to generate action potentials (Krnjević and Schwartz 1967). The cell should be able to discharge if excitatory inputs overcame the muscimol-induced inhibitory effects. Consistent with this was our observations that electrical stimulation in the SC after an injection of muscimol still evoked saccades at current levels similar to those used before the injection.



C SACCADE AMPLITUDE



The effects on saccade initiation of SC inactivation by a local anesthetic were similar to the effects of a GABA agonist. Soon after either type of injection, saccadic amplitude was reduced and saccadic latency was sometimes increased. Peak velocity was reduced even when this velocity was plotted as a function of the amplitude of the saccade actually made. These deficits were selective for saccades to the area of the visual field related to the movement fields of cells adjacent to the injection site. Thus, the present study, as well as our previous study (Hikosaka and Wurtz 1985) using muscimol as the injected substance, supports the idea that a particular saccade vector (direction and amplitude) is determined by a specific region of the SC (see Sparks and Pollack 1977; Wurtz and Albano 1980). SC cells outside this region would have little to do with the saccade.

This localization is particularly striking when the anesthetic acts on an area of SC related to perifoveal regions. In this case (as shown in Fig. 6) the monkey is able to saccade across the area of the field related to the anesthetized SC in order to make accurate saccades to more peripheral targets. This observation rejects any notion that longer saccades are dependent upon input from the movement fields required for smaller saccades.

The disruption of the amplitude of the saccades following ablation of the SC has previously been reported to be small. A slight decrease in the amplitude of saccades made to visual targets was revealed by an increase in the number of corrective saccades following partial ablation of the SC (Mohler and Wurtz 1977). After ablation of SC, monkeys also made fixations on pieces of apple that were less well centered (Schiller et al. 1980). The deficits reported here lend further support to the argument that the SC deficits studied in the past have been a combination of the ablation related deficit and compensation for that deficit (see Hikosaka and Wurtz 1985 for more detailed discussion). The severity of the deficit also suggests that in the normal monkey alternative

Fig. 6A-C. Effects of a lidocaine injection into the right SC related to an area near the fovea. **A** and **B** superimposed traces of saccades to visual targets before (**A**) and 5 min. after (**B**) an injection of lidocaine. Target positions were 5°, 10°, and 20° on the horizontal meridian to the right (upward) and 5°, 10°, and 20° on the left side (downward). Note that saccades to the target 5° on the left side became shorter while those to the target 10° on the left side were only delayed. Same organization as Fig. 1. **C** Visual field area showing a change in amplitude following injection. Only the amplitude of the first saccade made to each target point is shown, and the change is expressed as a percentage of the pre-injection value. Note that the greatest effect is on 5° saccades to the left while larger saccades were minimally affected. Injection was 6 µg of lidocaine in 1.2 µl saline solution. Same organization as Fig. 3

structures, such as the frontal eye fields, may have little function in the initiation of saccades to visual targets.

The decrease in saccadic amplitude following lidocaine injection was not always accompanied by an increase in latency (as in Fig. 3). This separation is particularly interesting since an increase in latency has been the most consistent deficit following ablation of the SC.

The reduction in saccadic velocity following injection of an anesthetic into SC is more surprising. This decrease in velocity is present even when the reduced amplitude of the saccade actually made is taken into account, a factor not considered in the previous qualitative comments on reduced velocity following ablations of the SC (Wurtz and Goldberg 1972b; Schiller et al. 1980). This effect on velocity is somewhat unexpected in view of a current neural model for saccade generation (Robinson 1975) in which the time course of a saccade is determined by mechanisms presumably located in the lower brainstem rather than in the SC.

Both the decreased amplitude and velocity of saccades following chemical lesions of the SC raise questions about the nature of the transition between the SC and the brainstem cells involved in saccade generation. The behavior of brainstem burst neurons, which are considered to provide extraocular motoneurons with excitatory or inhibitory inputs (Hikosaka et al. 1978; Igusa et al. 1980), is fundamentally different from saccade-related SC neurons: the number of intraburst discharges is almost linearly correlated with the horizontal or vertical amplitude of a saccade, while the instantaneous discharge frequency is linearly correlated with the instantaneous horizontal or vertical velocity (Henn and Cohen 1976; King and Fuchs 1979; Van Gisbergen et al. 1981; Kaneko et al. 1981; Yoshida et al. 1982). The discharge pattern of a burst neuron, therefore, uniquely predicts the horizontal or vertical component of a saccade, which is not the case for SC neurons. In contrast, SC cells discharge in relation to saccades to one part of the field (the movement field) and frequency and deviation of the discharge indicates proximity of the saccade to the best part of the field. A change in the way that saccade-related signals are carried in the SC cells and in the brainstem burst neurons must take place between these structures.

A simple hypothesis to explain this transformation is that a brainstem burst neuron receives excitatory inputs from many saccade-related neurons in the contralateral SC although this input may not be monosynaptic (Raybourn and Keller 1977). The rates of inputs from different areas within the SC to the

burst neurons might depend upon the neuron's relative contributions to horizontal and vertical saccades as suggested by McIlwain (1982). For example, suppose that lidocaine is injected into an area of the SC related most strongly to a 10° horizontal saccade. If the monkey tries to make a substantially shorter or longer saccade, burst neurons would receive normal inputs from SC neurons because they are located outside the area where lidocaine was infiltrated, and the resultant saccade would be normal. If the monkey tries to make a 10° saccade, the inputs to the burst neurons would be substantially decreased, although they may not be abolished because the surrounding cells which are unaffected by the anesthetic might contribute to the inputs. Such reduced inputs would be translated into a decrease in the amplitude of the total EPSPs, and then into a decrease in the frequency and the total number of spikes. The outcome would be a saccade with both a decreased velocity and amplitude.

An additional input to the burst cells is from the omnipause neurons located near the midline of the pontine tegmentum (Keller 1974). A pause in discharge of these neurons should be an important determinant of the duration, amplitude, and possibly velocity of a saccade, and the SC might alter the discharge pattern of the omnipause neurons as suggested by Raybourn and Keller (1977). A possible way in which a change in the SC could alter saccadic velocity in the absence of any change in amplitude is through the omnipause as has recently been suggested by Carl and Wurtz (1985). In this scheme, if SC input was important to activate the pause, failure to do so completely (a "leaky" pauser) could lead to incomplete release of the burst cells from inhibition, a reduced burst frequency, and consequently a reduced saccadic velocity.

Previous studies have shown a decrease in frequency of spontaneous saccades (Albano et al. 1982) or a restriction of the area where the gaze was directed (Schiller et al. 1980) after a large ablation of the SC. We observed no apparent effects of lidocaine in the SC on spontaneous eye movements. This might simply be because the inactivated area was so restricted. A larger reversible inactivation of the SC using muscimol (Hikosaka and Wurtz 1985) produced striking changes in spontaneous eye movements including an ipsilateral shift in eye position and horizontal nystagmus.

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Received May 11, 1985 / Accepted August 12, 1985