Modification of Saccadic Eye Movements by GABA-Related Substances. II. Effects of Muscimol in Monkey Substantia Nigra Pars Reticulata

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SUMMARY AND CONCLUSIONS

1. The preceding study (21) showed that a γ-aminobutyric acid (GABA) agonist or antagonist injected into the superior colliculus (SC) disrupted saccadic eye movements. The purpose of the present experiments was to determine whether this result was due to altering the inhibitory input to the SC from the substantia nigra pars reticulata (SNr).

2. SNr cells are themselves inhibited by GABA. Injection of muscimol, a GABA agonist, into the SNr should increase the inhibition acting on SNr cells and should reduce the inhibition acting on the SC. If the effects of GABA inhibition in the SC results from terminals originating in the SNr, muscimol in the SNr should act like bicuculline in the SC.

3. Muscimol in the SNr has the same general effect as bicuculline in the SC. The monkey made irrepressible saccades toward the contralateral visual field where cells in the SNr at the injection site had their visual or movement field. During visual fixation saccadic jerks occurred, interspersed with spontaneous saccades, instead of saccades to visual targets or to remembered targets. Saccades to remembered targets were more vulnerable to these saccadic intrusions than were saccades to visual targets.

4. Since muscimol in the SNr acts like bicuculline in the SC, we conclude that a substantial fraction of GABA-mediated inhibitory inputs in the SC originates from the SNr.

5. These experiments, in conjunction with previous experiments, show that the SNr exerts a tonic inhibition on saccade-related cells in SC and that this inhibition is mediated by GABA. The role of the SNr in initiation of saccades to remembered targets is particularly important since these saccades are more severely disrupted by muscimol in the SNr as well as in the SC.

6. We suggest that both of these conclusions about eye movement might apply to skeletal movements as well. First, the basal ganglia contribute to the initiation of movement by a release of the target structure from tonic inhibition. Second, this mechanism is particularly critical of the movements based on stored or remembered signals that are not currently available as incoming sensory inputs.

INTRODUCTION

In the preceding paper (21) we demonstrated that a γ-aminobutyric acid (GABA) agonist or antagonist injected into the monkey's superior colliculus (SC) disrupted saccadic eye movements. Muscimol (a GABA agonist) delayed, slowed, or shortened saccades made to visual or remembered targets. Bicuculline (a GABA antagonist) facilitated initiation of saccades and produced irrepressible saccades. Our logic in using these GABAergic agents was to artificially intensify the presumed GABA-mediated inhibitory inputs from the substantia nigra pars reticulata (SNr) to the SC by muscimol or suppress the action of these inputs by bicuculline.

It is possible, however, that other afferent connections to the colliculus or other neurons within the colliculus also use GABA as a
FIG. 1. Logical similarity of an injection of muscimol into the substantia nigra pars reticulata (SNr) and an injection of bicuculline into the superior colliculus (SC). Injection of a GABA agonist (muscimol) into the SNr should reduce its neural activity and release the SC cell from inhibition and increase its effect on brainstem oculomotor neurons (BS). Similarly, an injection of a GABA antagonist (bicuculline) into the SC should also release the SC from inhibition and should increase the discharge of brainstem oculomotor neurons. Open and filled circles represent excitatory and inhibitory neurons, respectively. Thick arrows indicate a high discharge rate.

neurotransmitter and that muscimol and bicuculline act on the receptors for these synapses rather than or in addition to the receptors for the nigrocollicular synapses. It is also possible that, unlike the rat (5), the transmitter released by the nigrocollicular connections in the monkey is not GABA.

An obvious way to resolve this issue is to manipulate cellular activity within SNr rather than in the SC. Such manipulation can be done by injecting GABA agonists or antagonists into the SNr since it is likely that many cells in the SNr are themselves inhibited by the same transmitter, GABA. The SNr has the highest concentration of GABA in the brain (12, 32); a large portion of the afferent fibers from the striatum is thought to be GABAergic (10, 14).

The purpose of the present experiments was to reduce the activity of SNr cells by injecting muscimol into SNr and then to examine the effect on saccadic eye movements. This is shown schematically in Fig. 1. Muscimol in the SNr should act on GABA receptors of SNr cells and should suppress their tonically high rate of discharge. If these cells have inhibitory connections with SC cells, SC should then be released from tonic inhibition, and saccade initiation should be facilitated (Fig. 1, right). Our prediction, therefore, is that the effects of muscimol in the SNr should be similar to those of bicuculline in the SC (Fig. 1, left). The present results show that this prediction is correct.

METHODS

The same two monkeys described in the preceding paper (21) were used in these experiments. Procedures for behavioral control, chemical injection, and data analysis were identical to those in the preceding report.

We made six injections into the SNr, and they are summarized in Table 1. We injected muscimol in the area of the SNr where cells with visual or saccade-related inhibitory responses were clustered, and these always were found in the dorsolateral part of the SNr (17). Entrance of the pipette tip into the SNr from above was indicated by a sudden increase in neural activity and the isolation of cells with tonic, rapid discharge rate. The injection usually was made <1 mm below the dorsal border where, if possible, single cells with visual- or saccade-related activity were recorded. The sites of two injections (J234, J9, see Table 1) were marked by passing currents through the

| Muscimol, | Conc., | Injection | Side | Direction of | Time Course, |
| μg | μg/ml | No. | | Facilitated Saccades | 1st sign/start recovery |
| 2.0 | 1.0 | J210 | L | R & U | *7.5 h |
| 4.0 | 5.0 | J219 | R | L & U | 14 min/5.5 h |
| 4.0 | 5.0 | J224 | R | L & U | 24 min/8 h |
| 1.2 | 1.0 | J227 | L | R & U | 1 min/9 h |
| 0.24 | 0.2 | J234 | L | R & D | 6 min/7 h |
| 1.2 | 1.0 | J9 | L | R & U | 2 min/7 h |

* First monkey; b, second monkey. L, left; R, right; U, up; D, down. * Onset time unclear because multiple small injections were made. † Experiment was not followed beyond 3 h.
TABLE 2. Control injections

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Amount, μg</th>
<th>Conc., μg/μl</th>
<th>Injection No.</th>
<th>Side</th>
<th>Structure</th>
<th>Time Course, 1st signifcant recovery</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscimol</td>
<td>1.2</td>
<td>1.0</td>
<td>66</td>
<td>L</td>
<td>SN pars compacta</td>
<td>1 h*</td>
<td>D deviation of eyes R-D saccades</td>
</tr>
<tr>
<td>Muscimol</td>
<td>4.0</td>
<td>5.0</td>
<td>/222</td>
<td>R</td>
<td>1 mm above SNr</td>
<td>1.25 h/8.25 h</td>
<td>L-U saccades</td>
</tr>
<tr>
<td>Muscimol</td>
<td>1.2</td>
<td>1.0</td>
<td>/220</td>
<td>L</td>
<td>3 mm above SNr</td>
<td>3 h*</td>
<td>No effect</td>
</tr>
<tr>
<td>Muscimol</td>
<td>1.2</td>
<td>1.0</td>
<td>/220</td>
<td>L</td>
<td>3 mm below SNr (cerebral peduncle)</td>
<td>13 min*</td>
<td>R-U saccades</td>
</tr>
<tr>
<td>Muscimol</td>
<td>1.2</td>
<td>1.0</td>
<td>b/10</td>
<td>L</td>
<td>1 mm above SNr</td>
<td>13 min*</td>
<td>No effect</td>
</tr>
<tr>
<td>Saline</td>
<td>2.0 μl</td>
<td></td>
<td>/231</td>
<td>R</td>
<td>SNr</td>
<td></td>
<td>No effect</td>
</tr>
</tbody>
</table>

j, First monkey; b, second monkey. L, left; R, right; U, upp; D, down. * Experiment was not followed to recovery.

The amount of injected muscimol ranged from 0.24 to 8.0 μg (Table 1). The effects on eye movements were qualitatively the same across these injections, and we did not notice a clear dose-response relationship within this range of doses. An injection of saline in the SNr produced no effects (Table 2).

RESULTS

Injection of muscimol in the SNr facilitated initiation of saccades to the contralateral side. We use one injection made into the right SNr (/224) as an example of the consistent effects obtained. For consistency, we show an example of the changes with saccades to visual targets first, even though these deficits are considerably smaller than those for saccades to remembered targets. The other injections are listed in Table 1.

Effects on saccades to visual targets

Effects of muscimol on visually evoked saccades were small but consistent. Figure 2 shows a vector plot of trajectories of saccades to visual targets at 10 and 20° eccentricity (left and right). Records show saccades obtained in the saccade task before (A) and 1 h, 15 min after (B) or 2 h, 43 min after (C) an injection of muscimol into the left SNr that would be expected to affect saccades made to the right visual field at 25 min after the injection of muscimol (Fig. 2B). No apparent changes were seen, but after 2 h, 43 min, the trajectories of both 10 and 20° saccades to the lower right were disrupted (Fig. 2C). The monkey tended to make inappropriate saccades to the contralateral side, leftward and upward, particularly when the target appeared in the lower-right quadrant. Note that only the first saccade is shown; once the eye moves, the visual target no longer falls in the same area of the visual field. The monkey did make subsequent saccades to acquire the target.

After the injection, latencies decreased slightly for leftward saccades (those toward the contralateral field) but increased for rightward saccades (those toward the ipsilateral field). In addition, there was a slight decrease in amplitude of saccades to the target 20° on the right. Peak velocities of saccades were not significantly altered (Fig. 3A). Thus, whereas the direction of the deficit in saccades to visual targets following muscimol injections into SNr is the same as that following bicuculline injections into SC, the effects in the SNr are smaller. These effects all become more evident when saccades to remembered targets are examined.

Effects on saccades to remembered targets

Saccades made to remembered targets showed deficits that were more severe and appeared sooner after the injection than was the case for saccades to visual targets. Figure 4 shows saccades to remembered targets in the delayed saccade task before (A) and after (B and C) the same muscimol injection in
FIG. 2. Trajectories of saccades to visual targets before (A), 1 h, 15 min after (B), and 2 h, 43 min after muscimol injection into right SNr. Left and right columns show saccades to visual targets with eccentricities of 10 and 20°, respectively. Eye positions are displayed for period from onset of target point until end of first saccade. Two saccades made to each target point are superimposed. Distance between two corners of each square represents 40°. Time interval between dots is 2 ms. A clear tendency to make incorrect, left-upward saccades is seen in C. Eye movements shown in Figs. 2-7 were obtained following saline injection (j/224).
FIG. 3. Relation of peak velocity of leftward saccades to their amplitude before (filled circles) and after (open triangles) muscimol injection in the right SNr. A: saccades to visual targets. B: saccades to remembered targets. Saccades used were those directed toward area of contralateral visual field most affected by injection between 135 and 225° where 0° is on right (see Ref. 21 for method of calculation).

the right SNr. Saccade latencies, which were virtually identical before the injection (Fig. 4A), were now separated into two groups 30 min after the injection (Fig. 4B); latencies decreased for leftward (contralateral) saccades, but increased for rightward (ipsilateral) saccades. A slight decrease in amplitude of 20° rightward saccades was also evident (Fig. 4B).
By 1 h, 30 min after the injection, saccades to remembered targets (Fig. 4C) were severely disrupted. After the fixation point was turned off the monkey at first made a saccade to the left side even if the target cue had been flashed on the right. In addition, the monkey sometimes made premature saccades to the left side immediately after or even before the fixation point was turned off. It should also be noted that at this stage the monkey was still able to make saccades to visual targets reasonably well (see Fig. 2B). In fact, when the target came on (right vertical line in Fig. 4C) the monkey corrected his eye position by making saccades to the visual target with fairly short latencies.

Unlike saccades to visual targets, clear increases in peak velocity were seen for saccades to remembered targets (Fig. 5B). The increases in peak velocity of leftward saccades in relation to their amplitude show that muscimol in the SNr raised the velocity of the memory-evoked saccades to the contralateral side so that the normally lower velocity of memory-evoked saccades became more equal to the velocity of normal visually evoked saccades (Fig. 3A).

Figure 5 shows the superimposed trajectories of the first saccade made after offset of the fixation point in the delayed saccade task. Before the injection (PRE), trajectories to targets 10° (Fig. 5, left) and 20° (Fig. 5, right) from the fixation point were fairly symmetrical. One hour and 30 min after the injection (POST, when effect was greatest as in Fig. 4C) saccades were rarely directed to the right (ipsilateral) side. Of 16 saccades made to each of the targets (2 trials × 8 directions), the monkey made the first saccade to the right side only twice. Furthermore, the trajectories of the remaining saccades deviated as if they were deflected from the right side. Leftward saccades were straighter and had larger amplitudes than those before the injection. These trajectories might be regarded as the weighted average of the signals generated by the injection and by the remembered targets.

Fig. 4. Effects of muscimol in right SNr on saccades to remembered targets. Saccades to remembered targets (delayed saccade task) before (A), 30 min after (B), and 1 h, 30 min after (C) injection. Saccades to 3 points on right horizontal meridian (5°, 10°, 20°) and symmetrical points on the left are shown. Traces show the first of the two saccades made to each point. Left and right vertical lines indicate offset of fixation point and onset of target point, respectively. Upper traces are horizontal eye po-

sitions (right is upward, and left downward); lower traces are vertical eye positions (up is upward, and down downward). Changes in latency (B) and direction (C) of saccades are evident after injection.
The tendency to make contralateral saccades after muscimol injection in the SNr was most readily revealed by the irrepressible saccadic jerks occurring during the fixation period of the delayed saccade task. Figure 6A shows the fixation period from the time of the target-cue presentation until the fixation point went off. Eight trials are superimposed. The monkey broke fixation frequently by making saccades away from and then back to the fixation point during the fixation period; he did not do so before the injection. The directions of the first saccades were exclusively to the left hemifield, particularly to the left and up, as demonstrated in Fig. 6B. The saccade jerks were more frequent after the target cue was flashed in the left hemifield and turned out to be the most sensitive, qualitative measure of muscimol effects in the SNr, appearing first from 3–25 min after muscimol injection.

Relation of muscimol effects to SNr and SC cell activity

The direction and amplitude of saccades facilitated by the injection of muscimol roughly corresponded to the area of the visual receptive field or movement field of cells at the point of injection. This comparison was difficult to make, however, because SNr cells were extremely sensitive to muscimol, which probably leaked out of the pipette tip. In most attempts cells became silent before the measurement of saccades was completed. We
were able to compare visual receptive fields and movement fields in only two cases. In both cases, the fields were large and centered in a contralateral quadrant of the visual field. The decrease in latency after an injection of muscimol at this point was centered on this quadrant of the visual field.

For one injection of muscimol in the SNr (J219), we kept recording the activity of a saccade-related cell in the intermediate layers....
of the ipsilateral SC throughout the period before and after the injection. Before the injection the cell was nearly silent (while the monkey was fixating but before any target came on), but after the injection the discharge rate increased to 12.5 spikes/s. The increase is consistent with a release of the SC cell from tonic inhibition exerted by SNr cells.

**Effects on spontaneous eye movements**

The tendency to make contralaterally directed saccades was evident in spontaneously occurring saccades as shown in Fig. 7. The left column in Fig. 7 shows the trajectories of these saccades, and the right column shows saccades aligned as if they started in the center of the display. Before the injection, in dim light, the eye scanned an area that included the center of the orbit (Fig. 7A, right). This area was largely within the central 40 degrees with a slight deviation to the right. As demonstrated by the display in Fig. 7A, left, the directions of spontaneous saccades were almost uniformly distributed in all directions. Figure 7B shows spontaneous eye movements recorded in total darkness 45 min after the injection. Eye position shifted to the left and up (Fig. 7B, left), and saccades were directed primarily to the left and up (Fig. 7B, right).

Spontaneous eye movements 3 h after the injection (and in dim light, the condition of the preinjection records), are shown in Fig. 7C. The area scanned by the eye was shifted to the left and slightly up. The eye rarely crossed the midline to the right, although objects in the experimental room were visible and investigators, though out of sight, were sitting beyond the edge of the right hemifield. In a typical sequence of eye movements, the monkey first made a brisk saccade to the left, immediately returned his eye with a slower saccade to the left, and then with a longer pause started a new cycle. Therefore, for the vector displays (Fig. 7C, right), we eliminated saccades that were followed by intersaccade intervals of <200 ms. We selected 200 ms, because it was close to the latency we observed for the monkey to make an active, voluntary saccade. The results were very clear. Twenty-two out of 36 saccades ended in the upper-left quadrant, whereas only 6 ended in the right hemifield (Fig. 7C, right). This display also demonstrates how brisk and straight the right-upward saccades were compared with those before the injection.

Usually more than 3 h after an injection involuntary slow drift of the eye appeared as the monkey sat in dim light, although it was present at earlier times if eye movements were recorded in total darkness (Fig. 7B). The slow drift then became faster, and turned into nystagmus. The direction of the nystagmus was usually horizontal, with the quick phase to the side contralateral to the injection and slow phase to the ipsilateral side. What was usually evident was that the eye did not move to the edge of the orbit but rather moved to a position in the contralateral field and stayed centered in that area. Thus, the effect on eye position of muscimol in the SNr was similar to that of bicuculline in the SC (21).

The monkeys appeared alert and comfortable throughout the recording sessions after an injection. They showed no sign of discomfort even when the nystagmus was severe, and were always anxious to eat monkey pellets. Frequently, we checked to see if they had any sign of sensorimotor disorder. We did not notice any involuntary skeletal movements, involuntary contraction of the neck muscles, or gross signs indicating that the monkeys had longer or shorter reaction times to release their hands from the bar. The monkeys had no difficulty in drinking or licking water, eating or chewing food pellets, or retrieving food pieces from their mouth pouches.

In one experiment (B9) we returned the monkey to his cage 3 h after the muscimol injection to see if there was any abnormality in body orientation or movements. The injection was on the left side, and his eyes stayed in the right-upper corner most of the time, and he bent his head slightly to the right. He had no difficulty or abnormality in walking or sitting. However, the monkey seemed to pay attention to his right side; he sat for several seconds looking at his right, and then reoriented himself to the right. This resulted in a slow rotation of the monkey’s body orientation.

**Control injections**

An injection of saline into the SNr had no effect (Table 2), as was the case with an injection of saline into the SC (21). For
FIG. 7. Spontaneous eye movements before (A), 45 min after (B), and about 3 h after (C) muscimol injection in right SNr. Records in A and C were obtained in dim light, whereas those in B were obtained in total darkness. Left column shows trajectories of eye position recorded in a period of 10 s. Right column shows trajectories of saccades recorded in a period of 30 s, and saccades are shown as if they started from center. Saccades that were preceded by inter-saccade intervals of <200 ms have been excluded. Numbers at the 4 corners of the display in right column indicate number of saccades that ended in corresponding quadrants. Center crosses in left column indicate primary position.
injections into the SC, however, the known maps of the visual and movement fields within the SC provided an indication of the spread of the chemical within the brain. No such built-in control was available to us for the injections within the SNr. We therefore made injections of muscimol in areas adjacent to the SNr as summarized in Table 2 to determine whether these injections gave effects identical with those seen in the SNr (Table 2). Figure 8 shows the sites of two control injections: one in the cerebral peduncle (solid arrow in Fig. 8A), the other in the substantia nigra pars compacta (SNc) (solid arrow in Fig. 8B). For the injection in the cerebral peduncle the pipette penetrated the lateral part of the SNr where a cell with a visual response was recorded. About 0.5 mm below this visual cell we encountered an area from which only positive short-duration spikes, indicative of fibers, were recorded. The injection was made 3 mm below the visual cell at the site where electrical stimulation through the microelectrode (8 μA) elicited a twitch in the right arm muscle. The tendency for rightward saccades appeared after 3 h (J230, Table 2).

For the injection into the SNc (Fig. 8B), we identified the area by the occasionally encountered spikes with long durations (2–3 ms), the low spike frequencies (usually less than 2 spikes/s), and the rhythmic background activity (17). After the injection the monkey looked somewhat drowsy, but showed no apparent changes in eye movements for the first hour. The tendency for right-downward saccades appeared after 67 min, and at the same time the eye deviated downward. In other control experiments we noticed neither additional effects on eye movements nor any effects on skeletal movements.

Four out of the five control muscimol injections (listed in Table 2) produced effects on eye movements similar to those seen after muscimol injections into the SNr. The time of onset of the effect, however, was more than 60 min after injection as compared to

FIG. 8. Sites of muscimol injections in and near the SNr of two monkeys. Hollow arrow in A: injection site in the SNr (J234). Filled arrow in A: injection site in the cerebral peduncle (J230). Arrow in B: injection site in the SNr (J06). SNr, substantia nigra pars reticulata; SNc, pars compacta; CP, cerebral peduncle; RN, red nucleus; LGNd, dorsal lateral geniculate nucleus. Scale mark is 1 mm.
much shorter onset times (<30 min) after the injections into the SNr (Table 1). The one exception was injection b10, which had an onset time of only 13 min, but was made only 1 mm above a SNr injection that used the same guide tube (b9, see Table 1). Even this short time was much longer than the onset time of 2 min for b9. The effects of all these injections outside the SNr also were weaker than those after the SNr injections. We conclude, therefore, that the effects on saccadic eye movements that we observe shortly after the injection of the SNr are probably due to the action of muscimol on cells in the SNr rather than to any action on cells in adjacent structures. For the long-term effects on spontaneous eye movements, however, we cannot exclude the possibility that some of the alterations are due to spread to other structures.

**DISCUSSION**

We demonstrated that a localized injection of muscimol (a GABA agonist) in the monkey SNr produces a strong tendency to make saccadic eye movements to the side contralateral to the injection. The time for the effects to appear after the injection was shortest when the injection was made at the exact site in the SNr where decreases occurred in the spike activity before saccadic eye movements. We consider the mode of action of muscimol in the SNr that might produce these effects, the role of the SNr in the control of eye movements, and what our experiments suggest about the role of the basal ganglia in the initiation of movement. We then discuss the relation of this eye-movement control in the monkey to the extensively studied circling behavior in rodents and, finally, consider several similarities between other observations and the eye movement deficits in diseases of the basal ganglia in man.

**Mode of muscimol action in the SNr**

This study was based on the assumption, reinforced by several lines of pharmacological evidence, that SNr cells are rich in GABA receptors. The concentration of GABA in the SNr is the highest in the brain for all mammals studied, including macaque monkeys (12, 32). A large fraction of afferent fibers from the striatum to the SNr is GABAergic (10, 14), and stimulation of the striatum produces inhibitory postsynaptic potentials (IPSPs) in cat SNr cells (66), which are depressed by picrotoxin (35). In the rat, SNr cells are much more sensitive to GABA than are SNC cells (43): iontophoretic injection of GABA suppresses spontaneous spike activity of SNr cells with less current than that required for SNC cells. We confirmed this result in the monkey (unpublished observation). It is, therefore, very likely that a small amount of muscimol, a potent GABA agonist, injected in the SNr hyperpolarizes the cell membranes, suppresses spike activity, largely reduces the output of the SNr, and releases cells in the intermediate layers of the SC from inhibition.

The effects of muscimol in the SNr were similar to those of bicuculline injections in the SC. There are irrefutable saccadic jerks to the side contralateral to the injection that occur interpersed with spontaneous saccades, during fixation of a visual target, instead of saccades to visual targets, and instead of saccades to remembered targets. There was a rough correspondence between the visual or movement field of an SNr cell near the injection site and the amplitude and direction of facilitated saccades after muscimol injection just as was the case following bicuculline in the SC. Saccades to remembered targets are the most vulnerable to these saccadic intrusions. Like bicuculline in the SC, the effects of muscimol in the SNr can be regarded either as a reduction of ionic inhibition or a perpetually present phasic process of inhibition that would signal a saccade to a visual or remembered target. The effect of this decreased inhibition in either case can be regarded as a motor “phosphenic” (21) competing with other signals imposing on the cells in the intermediate layers of the SC.

The salient point of these experiments is that, since muscimol in the SNr acts like bicuculline in the SC, we can infer that a substantial fraction of GABA-mediated inputs in the SC originates in the SNr. Saccades induced by bicuculline in the SC, however, were more uniform than those induced by muscimol in the SNr, and the onset time was shorter. These differences could be explained both by the fact that the SC is one step closer to the oculomotor output and that other GABA-mediated synapses in SC in addition to those from SNr might have
been blocked by bicuculline injections in the SC.

**Role of SNr in control of eye movements**

The present pharmacological experiments and the previous physiological and anatomic experiments allow us to draw two general conclusions about the role of SNr in the control of saccadic eye movements.

The first conclusion is that the SNr exerts tonic inhibition on saccade-related SC cells, and that this inhibition is mediated by GABA. This conclusion is based on a series of experiments. We had previously shown that cells in the SNr discharge rapidly but decrease their discharge rate either in response to a visual stimulus or before a saccade (17–19). These cells had visual-receptive fields or movement fields, and cells with similar visual or movement fields tended to cluster together in the SNr (17). We also showed that many of these visuooculomotor cells in the monkey SNr project to the ipsilateral SC, particularly to the intermediate layers where cells discharge before saccades to the movement field of the neuron (20). SNr cells project to the SC in a selective manner so as to match the visual or movement field of the SNr cells with the retinotopic map in the SC (20). Comparison of neural activity in the SNr with that in the SC suggested the inhibitory nature of the nigrocollicular connection; SNr cells pause as SC cells burst. Therefore, a reasonable interpretation of these observations is that the rapidly discharging SNr cells inhibit SC cells tonically, release the inhibition before saccades, and allow or facilitate a burst of spikes in SC cells.

Experiments reviewed in the preceding paper (21) suggested that GABA-mediated tonic inhibition is present in the SC; blocking GABA-mediated inputs in the SC by injection of bicuculline produced irreversible repetitive saccades to the contralateral side. The present study indicates, as we have already noted, that it is largely the SNr that exerts the GABA-mediated tonic inhibition on the SC.

The second major conclusion is that the SNr plays a particularly significant role in the initiation of saccades to remembered targets. Some SNr cells responded to a visual stimulus only when the monkey had to remember its position as a target for his later saccade; some cells decreased their discharge rate only before a saccade to the remembered position of a visual target (memory-contingent responses, 19). Other cells changed their discharge rate before saccades to visual targets (visually contingent responses), but such cells have been reported in the SC (30) and the frontal eye fields (4). After injection of muscimol into the SC, as well as into the SNr, saccades to remembered targets were more severely disrupted than were saccades to visual targets. Both the physiological and pharmacological results support the argument that SNr is particularly related to saccades based on spatial memory. Since activity of cells in the frontal eye fields is also altered when the monkey makes a saccade to a remembered target (4), the SNr might be the pathway by which such information is conveyed from the frontal cortex to the SC.

We have intended to use the term “saccades to remembered targets” as an operational description of saccades made in the delayed saccade task. A more general interpretation, however, might be that the behavior of these “memory-related” cells in the SNr and the behavioral deficits following injections into the SNr and SC reveal a role of this SNr in the initiation of saccades in the absence of direct sensory control. Saccades to remembered targets may be one example of “intentionally initiated saccades” that occur under a variety of conditions not yet tested.

**Implications for the function of the basal ganglia**

Our experiments have shown that the SNr, an output pathway of the basal ganglia, plays a major role in the control of eye movements. The other major output of the basal ganglia, the internal segment of the globus pallidus, is clearly related to skeletal movements (see Ref. 9 for review). This parallel organization of the two structures [or possibly of the same structure divided only by the internal capsule (31)] raises the question of how similar a role they might play in the initiation of movement, be it oculomotor or skeletal.

As in the SNr, most cells in the pallidum discharge rapidly and many of them change their discharge rate in relation to movements of the limbs, including many (but not all)
that decrease their discharge rate (see Ref. 9 for summary). Just as SNr cells produce inhibition in SC, pallidal cells monosynaptically inhibit neurons in the medial thalamus (42) which presumably have connections with frontal cortex neurons (11, 47). As in our hypothesis on the role of the SNr in the control of eye movement, these findings on the globus pallidus suggest a schema of the basal ganglia function that relies on a release of a target structure from inhibition (15, 34).

The cooling or ablation of the globus pallidus has been shown to reduce the reaction time of contralateral hand movements in the baboon (1) and to increase the electromyographic activity of both the flexor and extensor muscles leading to cocontraction or plastic rigidity in the monkey (23). These results may be analogous to the reduced latency for saccade initiation and the increased frequency of contralaterally directed saccades following muscimol injections in the SNr. Pallidal inactivation would lead to the facilitation of skeletal movements through a disinhibition of thalamic neurons, while nigral inactivation would lead to the facilitation of saccadic eye movements through a disinhibition of collicular neurons. Furthermore, inactivation of the globus pallidus by cooling disrupted self-paced elbow movements, while visual display improved the performance considerably (22). Although a number of interpretations are possible for this result, it has some similarity with our observation following inactivation of SNr cells by muscimol; memory-evoked saccades were disrupted more severely than were visually guided saccades. Thus the two major conclusions we have drawn on the relation of the SNr to eye movements might apply to skeletal movements as well: the basal ganglia contribute to the initiation of movements by a release of the target structure from a tonic inhibition; this mechanism is particularly critical if these movements are based on stored or remembered signals that are not currently available as incoming sensory inputs.

**Comparison of SNr injections in monkey and rodent**

Our observations on eye movements after injection of muscimol in the SNr have a similarity to the circling behavior in rats after such injections (2, 25, 26, 28, 33, 36). The most prominent behavior after muscimol injection is a turning of the body to the side contralateral to the injection. The rat typically turns its head toward its tail and rotates in a small circle. In addition, other types of stereotyped movements are sometimes observed, such as sniffing, gnawing, licking, etc. The contralateral turning is substantially reduced by a lesion of or a muscimol injection in the ipsilateral SC (25) suggesting the involvement of nigroctectal neurons. None of these studies reported changes in eye movements.

Whereas the monkey also showed a slight tendency for contralateral turning in his home cage after muscimol injections into the SNr, such injections produced primary rotation of the eyes. This difference in the drug effect between animals parallels the difference in normal behavior between these two animals. The monkey's eye has a well-developed fovea that enables fine analysis of visual objects, but to fully benefit from this evolutionary gain a well-developed saccadic system is required that moves his line of sight as fast as possible to center objects on the fovea. By contrast, the rodent's eye probably has an area centrals but no clear fovea (41), and consequently probably does not require such precise eye movements. This comparison implies a function for the SNr in orientation which is consistent throughout the species of mammals so far studied. The monkey would orient primarily by turning his eye (45); the rat would do so by turning his head or body. Muscimol in the SNr may artificially facilitate these mechanisms responsible for redirection of either the monkey's or the rodent's orientation.

**Relation of SNr to saccade deficits in Parkinson's and Huntington's disease**

Two diseases that involve the basal ganglia, Parkinson's disease and Huntington's disease, show alterations in saccadic eye movements. These diseases obviously involve more than just the SNr and its afferents, so that our experiments have only limited relevance, primarily related to the inhibition we have demonstrated of the SNr on the SC. In particular, the irreversible saccadic jerks we have observed after a reduction of this inhi-
bition are reminiscent of "square-wave jerks" seen in these diseases. Huntington's disease is characterized by difficulty in suppressing saccades especially to novel stimuli (27), and these square-wave jerks have a higher incidence in patients with Huntington's disease than in normal subjects (18). Frequent saccadic jerks in Parkinson's patients occur while they attempt to fixate (44). The irrepressible saccades after an injection of muscimol in the monkey SNr or an injection of biceuculline in the SC probably resulted from a decrease in the nigrocolliccular inhibition and a release of normally inhibited saccades. Square-wave jerks in patients with Parkinson's and Huntington's disease could logically be the result of a similar decrease in tonic inhibition. Square-wave jerks are also frequently observed with diseases of the cerebellum (24, 48) and this structure also provides tonic inhibition via the Purkinje cells onto the cerebellar and vestibular nuclei. It is interesting to speculate that prominence of square-wave jerks in disease occurs when the output of a structure that ordinarily produces tonic inhibition (such as the SNr or the cerebellum) is reduced.

Beyond this salient point, the relation between saccadic deficits in these diseases and our observations becomes less obvious. Quantitative studies of saccades in Parkinson's disease have generally shown a decrease in amplitude of saccades (6-8, 29, 37, 38, 40, 44), an increase in saccade latency (7, 37, 38, 44), and a decrease in saccadic velocity (37, 44), but not in all studies (29, 40). The velocity of saccades in Huntington's disease is also reduced (3, 27, 39). These characteristics would be expected to result from an increase in the nigrocollicular inhibition rather than the decrease we have suggested to explain square-wave jerks. A resolution of this paradox might well depend on an interaction of the tonic and phasic effects of the SNr on the SC or the change in action of the other structures involved in these diseases.

Our observations have also indicated that saccadic eye movements to remembered targets or those initiated in the absence of direct sensory input may be particularly dependent on SNr, and there is some indication that such a deficit may also be evident in Parkinson's and Huntington's diseases. For example, Flowers (13) found that the ability of Parkinson's patients to track a visual target that was sometimes blanked out for 2-4 seconds was impaired, and concluded that Parkinsonian patients do not spontaneously use prediction as readily as normals in controlling their actions. In Huntington's patients, difficulty in initiating saccades was most evident when a patient was asked to look in a particular direction rather than a specific visual target (27). These nonvisually-controlled movements had long latencies and were frequently accompanied by head thrusts or blinks.

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