CHAPTER 6

The basal ganglia

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1. Introduction: saccades and the basal ganglia

The substantia nigra first drew the attention of ocular motor scientists when its connection to the superior colliculus was demonstrated anatomically as well as electrophysiologically (Anderson and Yoshida, 1980; Graybiel, 1978; Hopkins and Niessen, 1976; Jayaraman et al., 1977; Rinivik et al., 1976; Vincent et al., 1978). Previous anatomical studies had shown terminal degeneration in the superior colliculus after lesion of the substantia nigra, but this was attributed to damage to corticocortical fibers that traverse the substantia nigra. New anatomical techniques utilizing axonal transport revealed that the origin of the tectal afferent fibers was in fact the substantia nigra (Beckstead et al., 1981; Bentivoglio et al., 1979; May and Hall, 1984).

This discovery was significant not only for ocular motor physiology but for an understanding of basal ganglia physiology as well. Until this time the substantia nigra was thought to play an important role in motor control through its dopaminergic connections to the neostriatum (caudate and putamen), which is the recipient portion of the basal ganglia. Since the substantia nigra receives massive connections from the neostriatum, this dopaminergic connection was thought to function as a feedback pathway for the regulation of the major output pathway from the neostriatum: from the globus pallidus to the central-medial thalamus (Cote, 1981). This scheme was brought into question by the discovery of non-dopaminergic neurons in the substantia nigra (Guyenet and Aghajanian, 1978). In fact, the dopaminergic and non-dopaminergic neurons are segregated to form two fairly distinct subregions, the pars compacta and pars reticulata. It is the non-dopaminergic pars reticulata, which we abbreviate as SNr, that sends efferent connections to the superior colliculus as well as to some regions of the thalamus.

The discovery of the nigro-collicular connection is also significant because it revived, at least partly, the old idea that the extrapyramidal system sends motor signals to the lower motor system independently of the pyramidal motor system (Jung and Hassler, 1960; Laurensen, 1963). This idea gained little support because anatomical studies revealed that the major output signal from one of the major segments of the basal ganglia, the globus pallidus, is directed to the part of the thalamus which may eventually join the pyramidal system (DeLong and Georgopoulos, 1981). The nigro-collicular connection, which did not involve the cerebral cortex, is therefore an important exception to this scheme, and this pathway might reveal motor signals which could be specific to the basal ganglia.

Still another implication of the nigro-collicular connection relates to clinical inferences about basal ganglia function. An influential view that the basal ganglia are related to slow movements while the cerebellum is related to fast (saccadic) movements (Kornhuber, 1971) came largely from the clinical
observations of eye movements. It was said that saccadic eye movements were impaired by lesions of the cerebellum but not by lesions of the basal ganglia. This notion was, however, questioned by clinical studies which showed disorders of saccadic eye movements in basal ganglia diseases (DeJong and Melvill Jones, 1971; Melvill Jones and DeJong, 1971). The discovery of the nigro-collicular connection served as an anatomical and physiological basis for these disorders of saccadic eye movements.

This nigro-collicular connection, however, is probably only a part of a larger system within the brain that is related to the initiation of saccadic eye movements. Fig. 1 outlines this system in the monkey, the animal on which most experiments related to saccades have been performed and on which we will concentrate in this review. In addition to the SNr, the basal ganglia include the caudate nucleus, which projects directly to the SNr. Other segments of the basal ganglia such as the globus pallidus, putamen and subthalamic nucleus are not shown since there is currently little evidence that neuronal activities in these areas are related to saccadic eye movements. The output of the basal ganglia is to the superior colliculus (SC). Among other targets (see Graybiel and Ragsdale, 1979), which in turn projects to brainstem areas related to the saccade generation (SG). The input to the basal ganglia relevant to saccadic eye movements includes a substantial projection from the frontal cortex as well as from other cortical areas such as the parietal cortex (Graybiel and Ragsdale, 1979; Percheron et al., 1984; Selemon and Goldman-Rakic, 1985). We have indicated the frontal contribution as arising from the frontal eye fields (FEF) and along the principal sulcus (PS).

In this chapter we will concentrate on the relationship of the SNr and caudate in the primate to the initiation of saccades. We will first describe the neuronal activity in the SNr related to the visual stimuli that evokes saccades, and then the activity related to the saccades themselves. We then consider the relation of the SNr to the superior colliculus both for normal neuronal activity and for the alteration in saccadic behavior that results when this connection is pharmacologically altered. We next describe the neuronal activity of a major input to SNr, the caudate nucleus. Finally we will briefly summarize several clinical observations relating basal ganglia activity to dysfunction of the saccadic system in man.

2. Substantia nigra pars reticulata (SNr)

2.1. Activity of neurons

Hikosaka and Wurtz (1983a,b,c,d) recorded single cell activity in the SNr of trained, alert monkeys. The behavioral methods used allowed analysis of both the sensory properties of SNr neurons and the relation of these neurons to the initiation of saccadic eye movements. The monkeys were trained to fixate their gaze on a small spot of light on a screen in order to obtain a reward (Wurtz, 1969). When -another spot of light (target point) appeared in place of the fixation point the monkey naturally moved his line of sight from the fixation point to the target point by making a saccadic eye movement.

We found SNr neurons that were related to eye
Over ten different types of response related to oculomotor activity have been observed in SNr (Hikosaka and Wurtz, 1983a). Sensory responses included those to spots of light and to clicks or tones. Modulation of these visual or auditory responses occurred depending upon conditions of fixation. Other changes in discharge rate within the SNr were related to sensory-motor activity such as saccades to visual targets. In this review we will limit our consideration to those responses related specifically to the visual-motor activity associated with saccades. We should also emphasize that any one SNr cell also might participate in several different responses. For example, a cell might have a response to visual stimulation, to auditory stimulation, and a change in discharge before a saccadic eye movement. One cell clearly carries several signals. We therefore will be referring to types of responses of SNr cells rather than to particular cells.

2.2. Enhanced visual responses

Saccades are frequently made to visual targets, and visual responses are among the most commonly observed responses in the SNr. For example, in the fixation task the SNr cell shown in Fig. 3A decreased its discharge rate when a target spot (T) came on in the visual hemifield contralateral to the cell's recording site while the monkey was fixing the central fixation point (F). The receptive field of this and most SNr cells was centered in the contralateral visual field, was more than a quadrant in size, but had a gradient of response within the field. Receptive fields in general were large and poorly demarcated, and they extended into the ipsilateral visual field. Cells tended to respond more vigorously to a smaller visual stimulus, at least in this experimental situation, and did not prefer particular stimulus features such as shape, color or orientation. The response was determined by the location of the stimulus with respect to the direction of gaze: if the location of the fixation point was shifted to the right or left, the receptive field was also shifted to the right or left. Thus, the visual receptive fields of the cells were in a retinal coordinate system.

Fig. 2. Characteristics of SNr cells. A. High rate of discharge shown in this histogram was obtained while the monkey was alert but before he began to fixate. B. The signal conveyed by cells in the SNr is a pause in activity shown here in response to the onset of a visual stimulus. In this and subsequent figures each cell discharge is indicated by a dot, successive presentations of stimuli or eye movements by successive lines, and the sum of these individual discharges is shown on the time histogram and the cumulative time histogram. Calibration for the histogram is 100 discharges/interval; bin width is 12 ms. Time between scale marks is indicated in the lower right corner. Subsequent figures use the same conventions. After Hikosaka and Wurtz (1983a).

movements or to sensory stimulation, and we observed several characteristics common to all these SNr cells. First, neurons had a high discharge rate, frequently in the range of 80–100 spikes/s, and this can be seen on the histogram of SNr discharge rates in Fig. 2A. Second, in the light of this high discharge rate, it is not surprising that the signal conveyed by the cells is a decrease in discharge rate. Fig. 2B shows that a decrease in the discharge rate followed onset of a target spot (T) in one part of the visual field. The dot pattern in Fig. 2B shows cell discharge in individual trials, and the histogram and cumulative histogram sum these trials. Finally, cells related to visual stimulations or eye movements tended to be in a restricted region of the SNr. This area was along the lateral edge of the SNr against the cerebral peduncle, the same area of the SNr which has been shown in the monkey to project to the superior colliculus (Beckstead et al., 1981; Francois et al., 1984).
A striking feature frequently seen in the visual responses of the SNr was their dependency on the behavioral context in which the visual stimulus was presented. Fig. 3B shows an example of such a behavioral contingency. The visual response was enhanced if the monkey made a saccade to the spot of light in order to detect the forthcoming dimming of the spot. Activity of the cell was silenced for several hundred milliseconds. That this enhanced response was related to selective use of this spot of light is shown by the experiment in Fig. 3C. If the monkey made a saccade to another spot of light remote from the target point (C in Fig. 3C), no enhancement was evident (compare 3C and 3A). In many cases the response when a saccade was made to a remote part of the visual field was less than when no saccade was made at all (again compare 3C and 3A). Auditory responses also showed the same enhancement when saccades were made to an auditory stimulus.

Enhancement of the visual response shown in Fig. 3B seemed to result from the summation of a movement signal with the visual response. This movement signal was time-locked to the onset of the saccade to the target point and was also manifest as a decrease in discharge rate. A separation of this response into sensory and movement signals can be demonstrated by using a task in which the target point was turned on while the fixation point remained on. After about a second the fixation point was turned off, and the monkey was allowed to make a saccade to the target point. Although for the particular cell shown in Fig. 3, the enhancement of the visual response could be explained by the summation of a visual response and a saccade-related response, the enhanced visual responses of other cells could not. Moreover, the reduced visual response shown in Fig. 3C cannot be explained by such a summation because the saccade alone was not accompanied by any change in response.

This spatially selective saccade-induced enhancement was first seen in the visual responses of superior colliculus neurons (Goldberg and Wurtz,
pressed until after the end of the saccade (for as long as several hundred ms). The decrease in discharge before saccades to visual targets is reminiscent of the increase in discharge before saccades to visual targets seen in the superior colliculus. Cells in both areas change their discharge before saccades and have movement fields centered on the contralateral visual field. SNr cells tend to have larger movement fields than do superior colliculus cells. What is strikingly different between the SNr and superior colliculus cells is that these SNr cells do not decrease their discharge rate before saccades made in the dark, whereas most superior colliculus cells do show such a change in discharge. These SNr cells are similar to a subset of intermediate layer colliculus cells described as visually triggered movement cells by Mohler and Wurtz (Mohler and Wurtz, 1976).

2.4. Memory-related responses

In the analysis of the discharge of SNr cells to visual targets, the monkey was required to fixate and then make a saccade when the fixation point went off and another target came on. By modifying this task, we uncovered what we believe is a salient characteristic of the activity of SNr neurons. The modified paradigm required the monkey to make a saccade not to a visual target that was present but to one that had to be remembered. In this delayed saccade task, the target was flashed briefly while the monkey was fixating, but the monkey was not allowed to break fixation as long as the fixation point was on. The monkey was therefore required to remember the target location and make a saccade to that location at a subsequent time when the fixation point went off.

Fig. 4 shows an example of an SNr neuron whose discharge rate decreased before and during such saccades to remembered targets. The left of Fig. 4A shows the response of the cell in the saccade task aligned on the onset of the target and the right shows the same response aligned on the onset of the saccade. There was only a slight decrease in discharge rate when the monkey made a saccade to the

1972). Subsequent studies on other brain areas using similar paradigms revealed that this phenomenon is not unique to the superior colliculus but is found in cerebral cortical areas, including frontal eye fields (Bushnell et al., 1981; Mohler et al., 1973), parietal cortex (Bushnell et al., 1981) and prefrontal cortex (Fisher and Boch, 1981), as well as subcortical areas such as the pulvinar (Petersen et al., 1985). Significant differences as to whether the enhancement is specific to the motor strategy (in this case, saccadic eye movement) with which the animal reacted to the stimulus exist between different areas (Bushnell et al., 1981; Goldberg and Bushnell, 1981; Mohler and Wurtz, 1976). Although this movement specificity was not studied for SNr neurons, the presence of saccade-induced enhancement suggests that the SNr plays a role either in attending to the stimulus or in initiating saccades to the stimulus.

The cell shown in Fig. 3 also illustrates the point that different types of activity (in the case of the cell in Fig. 3, visual and saccade-related responses) are combined in a single SNr cell. This may reflect the fact that an apparently simple motor signal is derived from different types of external and internal information.

Joseph and Boussaoud (1985) have shown that SNr cells in the cat also decrease their activity in relation to saccades to visual targets. The decrease in SNr cell activity may be related to a variety of movements comprising orienting behavior. By training the head-free monkey to make orienting movements, Lestienne and Caullier (1986) have shown a decrease in tonic firing rate for neurons in the medial SNr. The decrease started with an eye-head movement to direct the gaze to a target, and the decrease was further enhanced when a button was pressed to obtain a reward.

2.3. Saccade-related responses

Some SNr neurons also show a change in discharge related to saccades that are made to visual targets. The discharge rate decreases before onset of the saccade (as long as 80 ms before) and remains de-
target. No change in neuronal activity occurred when the monkey made saccades spontaneously without specific visual or remembered targets. When the monkey made the same saccade to the location of the remembered target as in Fig. 4B, a decrease in the discharge rate at the time of the saccade occurred (tick marks on the right). This decrease in discharge is clearer when the same single cell activity shown in Fig. 4B on the left is realigned on the onset of the saccade as it is in Fig. 4B right. This change in discharge is a saccade-related motor response in the sense that it is time-locked to saccades rather than to any other external event. But it is dependent on how the saccade is initiated.

Fig. 4. Discharge of an SNr cell before a saccade to the location of a previously flashed spot of light. In A, saccades to the visual target (T) were associated with only a slight decrease in discharge rate. In B, saccades with the same direction and amplitude but to the point where the target was flashed previously were associated with a clear decrease in discharge rate. The target was located 20° into the contralateral visual field. Each raster is aligned on an event: the onset of T (A, left), the offset of T (B, left), or the onset of the saccade (A and B, right). Vertical small bars on the raster in A and B (left) indicate onsets of the saccades. Note that the monkey failed to make a correct saccade on the first trial and, consequently, this trial is not shown in B (right). From Hikosaka and Wurtz (1983c).
Visual responses are also modified in some cells for saccades made to remembered targets. Fig. 5 shows the discharge of an SNr cell that had only a subtle response to a spot of light when it was presented in the fixation task (Fig. 5A) as a stimulus irrelevant to the monkey's behavior. This same stimulus produced a clear response (again a decrease in discharge rate) when it was presented as a target cue in the delayed saccade task (Fig. 5B). Since there was no change in the stimulus, what led to the enhanced response must be related to the monkey's commitment to use the stimulus cue. It should be emphasized that this type of cell showed no enhancement in the saccade task in which the

A

B

Fig. 5. Response of an SNr cell to a spot of light when the spot is remembered as the target for a saccade. A. Response to a spot of light (T) of short duration (50 ms) while the monkey looked at the fixation point (F) without making a saccade. The monkey was rewarded for release of the bar in response to the dimming of the fixation point (not shown). B. Clear response (a decrease in discharge rate) to the same spot of light (T) of the same duration when the monkey looked at the fixation point (F) but made a delayed saccade to the position of the flashed spot of light. The monkey was rewarded if he made a correct saccade after the fixation point went off. T was located 20° into the contralateral visual field in both A and B. Same organization as Fig. 4. From Hikosaka and Wurtz (1983c).
monkey made a saccade to the stimulus while the stimulus was still present. Therefore, this type of enhancement was different from the saccade-induced enhancement (Fig. 3) seen in several brain areas.

This selectivity for memory-dependent visual responses is in line with the memory-guided saccades shown in Fig. 4. It is as if one group of cells is related to the incorporation of visual information into memory and another is related to saccades based on that memory. Furthermore, both types of cells carry spatially specific information: memory-contingent visual cells as shown in Fig. 5 have visual receptive fields, while memory-contingent saccade cells as shown in Fig. 4 have movement fields.

The neural activity which might connect the above two response types, one being input to the memory and the other output from the memory, was also found in the SNr, and Fig. 6 shows an example. This type of cell shows a sustained decrease in discharge rate which starts after the target cue and continues until a delayed saccade occurs. This is the period during which the monkey must maintain the spatial information in order to prepare the saccade.

In the delayed saccade task the three types of nigral activity occur in sequence. Neurons that change their discharge in relation to the use of remembered targets are frequently unrelated to visually guided saccades or spontaneous, less purposeful saccades. The SNr neurons, as a whole, might be able to initiate and complete memory-guided saccades, a fairly complex behavioral sequence. Whether these activities are causally related to each other or induced by independent inputs from other brain areas is unknown, but preliminary experiments on the caudate suggest that the latter is more likely (as described in later sections).

There are also cells related both to visually guided and to memory-guided saccades, but not to spontaneous saccades. We should note that the decrease in discharge rate related to visually guided saccades does not precede saccade onset by as long a
time period as does that preceding memory-guided saccades. This might indicate that the SNr plays rather a minor role in the initiation of visually guided saccades compared with other brain areas like the frontal eye fields.

In summary, SNr cells show a high tonic rate of discharge and decrease their activity in relation to the preparation and initiation of purposeful, voluntary saccades. Two major classes of saccade-related cells are present in the SNr, one related to memory-guided saccades and the other related to visually guided saccades, although there is considerable overlap between them. An important denominator of nigral neural activity is the dependence of the change in cell discharge on the behavioral context. In contrast, the physical properties of stimuli or eye movements are poorly represented. Particularly significant and characteristic of the SNr compared with other saccade-related brain areas is the prominent relation of cell discharge to saccadic eye movements based on short-term memory. Thus behaviorally contingent neural information carried by SNr cells is presumably transmitted to the superior colliculus to facilitate the initiation of saccades, and this next step will be described in the next section.

3. The nigral-collicular connection

3.1. Relation of SNr to SC

The role of the intermediate layers of the superior colliculus in the initiation of saccadic eye movements has been firmly established (see chapter 5 of this volume). Anatomical data have shown that a substantial fraction of the neurons in the monkey SNr project to these intermediate layers (Beckstead, 1983; Beckstead et al., 1981; Francois et al. 1984). However, cells with visual or saccade-related activities are concentrated in just a small part of the pars reticulata (Hikosaka and Wurtz, 1983a). The characteristics of other cells are largely unknown except for some relation to oral-facial movements (DeLong et al., 1983; Joseph et al., 1985; Mora et al., 1977; Nishino et al., 1985). Therefore, that the visual-motor cells in SNr project to the visual-motor cells in the superior colliculus could not have been inferred from anatomical data alone.

Hikosaka and Wurtz (1983d) addressed this question of the connection by using antidromic stimulation. They first determined the response types of a single SNr cell and then examined whether the nigral cell was activated antidromically by microstimulation of the superior colliculus. About half of the cells recorded in the lateral part of the SNr were activated antidromically with relatively low stimulus currents (less than 50 μA) and almost all of the antidromically activated cells showed visual or saccade-related activities. An example is shown in Fig. 7. The stimulating microelectrode was inserted through the guide tube which was implanted over the superior colliculus and, while cellular activity was recorded from the SNr, the stimulating electrode was lowered through the layers of the superior colliculus to determine the thresholds and latencies of antidromic responses. This experiment gave a picture of intra-collicular axonal arborization of SNr cells. For each SNr cell, more than one low-threshold peak was frequently found. Most commonly the low threshold was found in the intermediate layers, occasionally in the deep layers and only rarely in the superficial layers. This suggests that the visual or saccade-related SNr cells terminate preferentially in the intermediate layers. The latencies of antidromic spikes decreased as the stimulating electrode was lowered through the colliculus, which suggests that axons of SNr cells enter the superior colliculus through the deeper layers.

The stimulating electrode was then used for recording superior colliculus neuronal activity, and saccade-related burst cells were recorded frequently near the lowest threshold points on a penetration. Fig. 7 compares the discharge of an SNr cell (top) with that of a superior colliculus cell (bottom). The colliculus cell was recorded at the point from which the nigral cell was activated with the lowest stimulation current, and this colliculus cell therefore might have received synaptic connection from that nigral cell. In Fig. 7 the discharges of these cells are aligned
on visually guided saccades (A) or memory-guided saccades (B). A striking feature in Fig. 7B is the closely related time course of the SNr and superior colliculus cell activity: the discharge of the SNr cell decreased while the superior colliculus cell increased before the saccades. This mirror-image-like relationship suggests the inhibitory nature of the presumed nigro-collicular connection: the SNr cells exert tonic inhibition on superior colliculus cells, and facilitate the initiation of a saccade by a release from this tonic inhibition.

This simple scheme, however, fails to explain the dissociation of these cells in the case of visually guided saccades (Fig. 7A). The saccade-related change in activity of the SNr cell shown in Fig. 7 was greater for memory-guided saccades than for visu-

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**Fig. 7.** Correspondence of a decrease in SNr cell activity with an increase in superior colliculus cell activity in relation to memory-contingent saccades. The activity of an SNr cell (upper trace) is compared to that of a superior colliculus cell (lower trace). A shows activities related to a visually guided saccade (saccade with overlap task). B shows activities related to a memory-guided saccade. While the superior colliculus cell discharged before visually and memory-guided (and spontaneous) saccades, this SNr cell paused primarily before memory-guided saccades. From Hikosaka and Wurtz (1983d).
ally guided saccades, whereas the colliculus cell showed a similar burst of spikes in either condition. It follows that the burst activity of the colliculus cell cannot be explained solely by the release from inhibition induced by this type of SNr cell. Hikosaka and Wurtz (1983c) hypothesized that each type of SNr cell does not send a command but contributes to the initiation of saccades in a limited behavioral context. The convergence of different types of nigral input, in addition to other presumed excitatory inputs, notably from the frontal eye fields, could make up the motor signal. Whether a saccade is made intentionally to a visual target, or an auditory target, or a remembered target, or made spontaneously without particular targets, an almost identical burst of spikes is elicited in most saccade-related cells in the superior colliculus. The analysis of the nigro-collicular connection suggests that this strong, unconditional correlation of the superior colliculus activity with a motor output is in fact created by the convergence of behaviorally conditioned, heterogeneous inputs from several brain areas. This process seems to be reflected in the existence of cells in the superior colliculus which are related to saccades in a conditional manner, namely visually triggered saccade cells (Mohler and Wurtz, 1976).

Another important oculomotor signal to the superior colliculus arises from the frontal eye fields (Segraves and Goldberg, 1985), and saccade-related signals in the frontal eye fields are also conditional in that presaccadic neuronal discharges occur only when a purposeful saccade is made to visual or remembered targets (Bruce and Goldberg, 1985). Therefore, neither the SNr nor the frontal eye fields, which are the two major inputs to the superior colliculus, provide signals related to spontaneous saccades. Neural mechanisms underlying spontaneous saccades may lie in the lower brain stem areas possibly in or around the superior colliculus, although recent evidence suggests a possible role of the supplementary motor cortex (Schlag-Rey and Schlag, 1984).

Although the electrophysiological studies present a logical framework in which the SNr might participate in the initiation of saccades, it is still uncertain whether it actually has a role in the generation of saccades. The following pharmacological studies address this question.

3.2. Pharmacological manipulation of nigro-collicular connection

Several lines of experiments indicate that the nigro-collicular connection is mediated by γ-aminobutyric acid (GABA). The concentration of GABA is high in the superior colliculus (Fahn and Cote, 1968). After a lesion of the substantia nigra the concentration of glutamic acid decarboxylase (GAD), which is a critical enzyme for the synthesis of GABA, decreases (DiChiara et al., 1979; Vincent et al., 1978). This suggests that the axon terminals of nigro-collicular cells contain GAD and are probably GABAergic. These terminals have recently been shown more directly by using the electron-microscope to identify terminals containing GAD or GABA transaminase synapsing on superior colliculus cells (Araki et al., 1984; Lu et al., 1983). That the superior colliculus cells receiving afferents from the SNr project to the lower brainstem or the spinal cord has also been demonstrated (Chevalier et al., 1984; May and Hall, 1984; Moschovakis and Karabelas, 1985). Stimulation of the SNr typically inhibits superior colliculus cell discharges, but this inhibition is blocked by iontophoretic application of a GABA antagonist (Chevalier et al., 1981b). Monosynaptic IPSPs are induced by stimulation of the SNr in different types of cell in the intermediate and deep layers of the superior colliculus. While EPSPs are occasionally seen in the superior colliculus following nigral stimulation, they are due to stimulation of cortico-tectal fibers in the cerebral peduncle (Chevalier et al., 1981a). Such a wealth of evidence has established the simple scheme that SNr cells exert GABAergic inhibition on cells in the superior colliculus.

This similarity of GABAergic inhibition across species does not necessarily indicate that the function of the nigro-collicular connection is the same across these species. For example, alteration of the
A  Cell discharge

B  

C  

D  

E  

100 msec

10 deg

15 spikes/trial

Latency of saccade

b3a - b3a

b3f - b3a

b3i - b3a

100 msec
SNr or of the SNr-superior colliculus connection produces circling behavior in rats. It is generally thought that rats orient their head and body rather than their eyes to an object attracting their attention and that their circling behavior reflects changes in head and body orientation. In contrast, in primates the role of eye movements in such orienting behavior is far greater than in rodents. Pharmacological manipulation of the nigro-colllicular system would therefore be expected to affect eye movements in the monkey.

In such pharmacological experiments, Hikosaka and Wurtz (1985a) injected small quantities of GABA-related substances into the superior colliculus or the SNr while the monkey was performing the visuo-oculomotor tasks already described, and found striking changes in saccade eye movements. Fig. 9 shows the effects of muscimol (a GABA agonist) injection into the superior colliculus. A glass pipette for drug injection was inserted through an implanted guide tube into the superior colliculus. The pipette contained a fine tungsten microelectrode which allowed recording of single or multiple cell activity at the site of the injection. In this case, the injection pipette was introduced into the left superior colliculus and the activity of a single cell was recorded which showed a burst of discharges before a saccade only when the saccade was directed right and downward (Fig. 8A). Electrical stimulation through the tungsten microelectrode elicited a saccade into this movement field (as indicated by the star in Fig. 8A, right). These results indicated that the tip of the injection pipette was located in the lateral region of the intermediate layers of the left superior colliculus, judging by the relationship to saccades made to the lower visual field. This location was later confirmed by histological examination.

A small amount of muscimol was then injected at this site, and the monkey became unable to make saccades to the targets in the right-downward direction, whereas leftward saccades remained normal. Fig. 8B shows saccades just before the injection, and Fig. 8C-E shows sequential change in saccades after the injection. Fig. 8B-E left shows superimposed traces of saccades to 6 targets in the right-downward quadrant. Fig. 8E right shows the change in latency of saccades to different areas of the visual fields. Saccade latencies were slightly elevated after the pipette had been positioned in the superior colliculus but before the injection (Fig. 8B), but the increase was limited to 4 target points in the right-downward direction. Shortly after the injection (Fig. 8C, 3 min) latencies of saccades to the right-downward targets were further prolonged (Fig. 8C), and 40 min later the monkey did not respond to these targets (Fig. 8D). It is striking that saccades to right-upward targets showed much smaller changes and those to left targets were never affected, suggesting that the injected muscimol remained relatively confined to the lateral part of the left superior colliculus. These results indicate that

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Fig. 8. Time course of changes in eye movements following an injection of muscimol in the left SC of a monkey. A. Activity of a single SC cell at the injection site. Left shows an averaged post-stimulus time histogram for the cell when the monkey made saccades to targets in lower right quadrant of the visual field. Vertical line indicates when fixation point went off and target point came on; height of ordinate indicates 100 spikes/trial. Right shows the movement field of the SC cell plotted on a polar plot of the visual field. Eccentricities of dashed circles are 5, 10, 15, 20°, R, L, L, D, right, left, up, down, respectively. Difference in number of spikes in the post-target period (0-400 ms after target onset) and that in the pre-target period (0-400 ms before target onset) was calculated for each trial and plotted at target position. Each data point is average of two trials. Asterisk indicates end point of stimulation-evoked saccades (threshold 9 μA). B-E. Sequential change in saccades to visual targets before and after muscimol injection. B. Data obtained after injection pipette had been introduced into left SC but before muscimol was pressure injected. Left shows superimposed traces of saccades to targets in lower right quadrant; upper trace, horizontal eye positions; lower trace, vertical eye positions. Right shows changes in latency of saccades compared with those before the pipette was introduced into the brain. Increase in latency is upward. C-E. Data obtained beginning 3 min (C), 40 min (D), and 7 h 45 min (E) after muscimol had been pressure injected. D shows that monkey could not make any saccade to most targets in lower right quadrant within the recording time (975 ms after target onset). From Hikosaka and Wurtz (1985a).
superior colliculus cells related to saccades are likely to have GABA receptors, and they suggest that GABA-mediated afferents are critically involved in the initiation of saccades. The use of muscimol also allowed comparison of the increased inhibition on saccades to visual and remembered targets. Fig. 9 shows an example of an injection of muscimol into the superior colliculus and its effect on saccades to visual targets (Fig. 9B) and to remembered targets (Fig. 9C). This injection used a smaller dose of muscimol and a more experienced monkey so that saccades to visual targets after the injection had longer latencies but approximately the same amplitude as saccades before. Saccades to remembered targets were inaccurate, suggesting that the SNr might be more involved with saccades to remembered than to visual targets.

Injection of a GABA-antagonist (bicuculline) into the superior colliculus (Fig. 10, left) induced repetitive, irrepressible saccades to the side contralateral to the injection. The monkey attempted to fixate the central spot of light to detect its dimming, which had been a trivial task before the injection, but became unable to do so because of the stereotyped saccadic jerks (Fig. 10, left and bottom). The direction and amplitude of the induced saccades corresponded to the movement fields of superior colliculus cells at the site of the injection, indicating that cells in a fairly localized area of the superior colliculus were excited. These results suggested that saccade-related superior colliculus cells not only have GABA receptors but also are actually under tonic GABA-induced inhibition exerted by the SNr.

Injection of muscimol in the SNr (Fig. 10, right) substantiated this idea. It had been demonstrated that the concentrations of GABA and GAD are high in the substantia nigra (Fahn and Cote, 1968; Okada et al., 1971), that cells in the substantia nigra, especially in the SNr, are extremely sensitive to GABA, and that their discharge is suppressed by iontophoretically injected GABA (Waszczak et al., 1981). Therefore, muscimol injected into SNr should suppress the otherwise high-frequency discharge of SNr cells, thus effectively eliminating the nigro-collicular connection. The result of such an injection was the production of irrepressible saccades to the side contralateral to the injection. These saccades were similar to those produced by the injection of bicuculline into the superior colliculus but somewhat less stereotyped (Fig. 10, right). This effect was more evident and appeared with shorter latent periods when the site of the injection was close to visual or saccade-related cells in the SNr. Similar results were obtained after injection of muscimol in the cat substantia nigra (Boussaoud and Joseph, 1985). These pharmacological experiments led to the conclusion that the GABA-mediated inhibition of superior colliculus cells is exerted by cells in the SNr and that this inhibition is necessary for the eyes to maintain fixation. The simplest explanation of the role of the SNr is that there are two ways in which the intermediate layers of the superior colliculus activate the brainstem saccade generator (SG). First, the nigra-induced tonic inhibition would keep the superior colliculus hyperpolarized. The removal of this in-

Fig. 9. Differential effects of injection of muscimol into the right superior colliculus on saccades to visual and remembered targets. A. Saccades evoked by electrical stimulation in the right superior colliculus before (left, 22 μA threshold) and after (right, 32 μA threshold) injection while the monkey was looking at the fixation point. Stimulation was a train of biphasic, negative-positive pulses (200 Hz, 50 ms) with each pulse 0.2 ms long. The vertical line indicates onset of stimulation. B. Saccades to visual targets before (PRE) and 6 min after (POST) injection of muscimol. Records for saccades to each of three different points on the right horizontal meridian (5°, 10°, 20°) and three on the left horizontal meridian are superimposed. Upper traces are horizontal eye positions (right is upward, left, downward) and lower traces are vertical eye positions (up is upward, down, downward). The vertical line indicates the time at which the fixation point went off and the target point came on. C. Saccades to remembered targets before (PRE) and 11 min after (POST) the same injection of muscimol into the right superior colliculus. The same saccade targets were used as in B and the left vertical line indicates offset of the fixation point and the right vertical line the onset of the target point. From Hikosaka and Wurtz (1986a).
Inhibition alone would induce a burst of spikes in the superior colliculus cells. The experiments by Chevalier et al. (1985) have demonstrated this possibility. Second, the disinhibition alone may not be capable of eliciting the burst of spikes in the superior colliculus cells but may allow incoming excitatory inputs from other brain areas to activate the superior colliculus cells.

The possibility of the interaction of excitatory and inhibitory inputs emphasizes the importance of the inputs to the intermediate layers of the superior colliculus. While some input may be from the superficial layers (Grantyn et al., 1984; Mooney et al., 1984) and the parietal cortex (Lynch et al., 1985), the two major inputs to the intermediate layers are from the frontal eye fields and the SNr (Illing and Graybiel, 1985; Karabelas and Moschovakis, 1985). Substantia nigra axon terminals show a patchy pattern and are largely restricted to the intermediate layers (Graybiel, 1978; Jayaraman et al., 1977; May and Hall, 1984), as are frontal eye field axon terminals (Illing and Graybiel, 1985). Illing and Graybiel showed that these two kinds of patches largely overlap, suggesting the convergence of these inputs on single superior colliculus cells. Using electrophysiological and HRP intracellular staining techniques, Karabelas and Moschovakis (1985) and Moschovakis and Karabelas (1985) indicated that such convergence does exist but not for every colliculus cell. Unlike the nigral input, that from the frontal eye field is likely to be excitatory and is usually inactive except for phasic increases.
Hence, either one of the two events, disinhibition from the SNr or excitation from the frontal eye fields, or a combination of these could produce a burst of spikes in superior colliculus cells, which would then drive the saccade generator to initiate a saccade. One possibility is that these inputs represent a direct and indirect pathway from the frontal eye fields to the superior colliculus. What is not known is whether there is a difference in the signal conveyed by these two pathways.

4. The caudate nucleus

The next question is what eliminates the nigrocollicular inhibition, in other words, which brain area produces the cessation of SNr cell discharges? The primary input to the SNr is the caudate nucleus, and we will now consider the discharge of neurons in this structure related to visual stimulation and eye movements.

4.1. Neural activity in the caudate nucleus

The neostriatum (caudate and putamen) is the recipient portion of the basal ganglia. It receives afferents from different areas of cerebral cortex and medial parts of the thalamus, and it projects largely to the globus pallidus and the substantia nigra (Carpenter, 1981; DeLong and Georgopoulos, 1981; Graybiel and Ragsdale, 1979). In the monkey this main pathway in the basal ganglia is roughly divided into two segments: one from the caudate to the SNr, and the other from the putamen to the globus pallidus (Feger and Crossman, 1984; Parent et al., 1984). Based on this anatomical information, the nature of the neural activity related to saccades was studied in the caudate nucleus to see if this region could plausibly be the source of the SNr activity.

Hikosaka and Sakamoto (1986) found that many caudate cells showed visual or saccade-related activities. Unlike cells in the SNr with their high discharge rate, caudate cells discharge only sporadically if the monkey is not performing a behavioral task. Also, in contrast to the SNr, the cells investigated during behavioral paradigms similar to those used for SNr showed an increased rate of discharge.

The activity of caudate cells can be grouped into three classes: (1) activity induced by visual stimuli, (2) activity time-locked to the onset of saccades, and (3) activity unrelated to sensory or motor events. Fig. 11 shows an example of saccade-related activity. In the saccade task (Fig. 11, left), this caudate cell showed little change in discharge, but in the delayed saccade task (Fig. 11, right) the cell started to discharge vigorously before the onset of the saccade. The activity of this caudate cell was therefore related to memory-guided saccades, but not to visually guided saccades. Spontaneous saccades in the darkness were accompanied by no significant change in discharge if the monkey did not actively search for something in the dark. The cell's activity was spatially selective in that it discharged only before saccades to the side contralateral to the cell's recording site. These characteristics are the same as for the memory-contingent saccadic activity in the SNr (see Fig. 4). The only difference is that the nigra cells decrease while the caudate cells increase their activity before the memory-guided saccades.

Similar mirror-image-like relationships between the caudate and the SNr were found for other types of activity. Thus, some caudate cells discharged in response to a visual stimulus but only when the monkey had to remember the position of the stimulus for a later saccade, in much the same way as did some SNr cells (see Fig. 5). Other caudate cells began to discharge after the target cue and the discharge rate increased until the saccade to the remembered target occurred, as did SNr cells such as that illustrated in Fig. 6. There were other types of cell in the caudate that were related to visually guided saccades rather than memory-guided saccades. But no cells were found that were consistently related to spontaneous, less purposive saccades, in agreement with a previous report (Matsunami and Cohen, 1975).

The above results strongly suggest that these caudate cells could be the origin of the visual and saccade-related activity in the SNr and that the action
Fig. 11. A caudate neuron with memory-contingent saccade activity. Left: no obvious discharges were present in the saccade task. Right: in the delayed saccade task, the neuron showed transient discharges before saccades to the same target which now was not actually present but just remembered. The onset of a saccade is indicated by a small vertical bar on each raster line. Saccades to the ipsilateral remembered target were accompanied by fewer discharges. Calibration indicates 50 and 100 spikes/trial. Reprinted from Fitkusaka and Sakamoto (1996).
of caudate cells on SNr cells is inhibitory. That the caudate-nigral connection is inhibitory and uses GABA as a neurotransmitter has been indicated by electrophysiological (Precht and Yoshida, 1971; Yoshida and Precht, 1971) and anatomical (Di-Chiara et al., 1980; Fonnum et al., 1978) studies. Anatomical studies have also indicated that medium-sized spiny cells, the most common morphological type, are the projection cells destined for the SNr or the globus pallidus (Grofova, 1975; Kitai, 1976, 1981) and that they contain a high concentration of GAD or GABA, suggesting that they are GABAergic (Bolam et al., 1985). Williams and Faul (1985) have shown that identified nigrostriatal cells receive monosynaptic inputs from the striatum. Chevalier and his colleagues (Chevalier et al., 1984, 1985) have demonstrated in the rat that the local excitation of caudate cells leads to striking inhibition of SNr, which in turn leads to the excitation of tecto-spinal cells through disinhibition.

4.2. Possible inputs to the caudate

The next step in relating the caudate to control of saccadic eye movements is to consider what the inputs might be. We can do this by briefly considering the structures projecting to the caudate, which include several areas of the cerebral cortex and parts of the thalamus.

Cortical inputs arise mainly from the association area including the prefrontal, orbitofrontal, parietal and inferotemporal cortices (Carpenter, 1981; Graybiel and Ragsdale, 1979; Kitai, 1981). These cortical inputs seem topographically organized (Goldman and Nauta, 1977; Ragsdale and Graybiel, 1981; Percheron et al., 1984; Yeterian and Van Hoesen, 1978). For example, Selemon and Goldman-Rakic (1985) have shown that cortical areas project to longitudinal territories which occupy restricted medial-lateral domains of the caudate and putamen: the posterior parietal area projects to the dorsolateral part of the caudate, dorsolateral prefrontal area projects to the central part, and the orbitofrontal, cingulate and superior temporal areas project to the ventromedial part.

Projection of the frontal eye-fields, which lies at the caudal-most part of the prefrontal cortex, is mainly to the body of the caudate and is also restricted in a longitudinal region close to its ventral border (Kunzle and Akert, 1977). The frontal eye fields could therefore provide the caudate with information tightly coupled with visual inputs or saccades (see chapter 7 of this volume). Other parts of the prefrontal cortex might provide information that is not directly related to such sensory-motor events but is related to expectation or short-term memory. One candidate for such a memory-related structure is the area around the principal sulcus. Lesion of this area is known to disrupt the monkey's performance of a delayed response task in which the animal is required to remember the position of one of two objects to obtain a reward hidden below the correct object (Battig et al., 1960; Butters and Rosvold, 1968; Iversen, 1979). Furthermore, some neurons in this area show tonic discharges during this task when the monkey remembers the location of the cued signal (Fuster, 1973; Kubota and Niki, 1971). Since the saccades to a remembered target task can be considered to be an oculomotor version of the delayed response task, it is plausible that the principal sulcus area is the origin of caudate activities related to short-term memory or expectation. However, the actual role of such cortical inputs remains to be studied.

The major source of the thalamic inputs is the intralaminar areas including the centromedian-parafascicular complex, nucleus centralis and nucleus medialis dorsalis (Carpenter, 1981; Graybiel and Ragsdale, 1979). These areas have traditionally been considered to be a rostral extension of the reticular activating system, but the role of the thalamus is certainly not limited to such a general function. Schlag-Rey and Schlag (1977, 1984) have demonstrated that cells in the intralaminar areas of the thalamus (nucleus centralis dorsalis, nucleus medialis dorsalis and nucleus centralis superior) show discharges in response to a visual stimulus or before saccades to a visual stimulus. These cells might project to the caudate (Cesar et al., 1985). Furthermore, there is anatomical evidence that the
SNr projects to the intralaminar thalamic areas (Carpenter et al., 1976; Linskey et al., 1985). Hence, the caudate, SNr and intralaminar thalamic area might form a neural circuit loop. It is well-known that the intralaminar thalamic area is interconnected with the frontal eye fields reciprocally (Orem and Schlag, 1971) and receives inputs from the intermediate layers of the superior colliculus (Schlag et al., 1974). Therefore, the actual scheme of inputs to the caudate from the thalamus and cortex might be much more complicated than consideration of separate anatomical inputs reveals.

5. Eye movement disorders of the basal ganglia

In this chapter we have attempted to summarize how the action of the SNr on the superior colliculus influences the generation of saccadic eye movements. This analysis at a neuronal level in the monkey has included the deficits that follow pharmacological disruption of the system. Such disruption of this basal ganglia system also occurs in several diseases of man, and in this last section we will consider possible interpretations of these deficits in man in the light of our knowledge of the monkey. Such a comparison is admittedly limited in the light of the limitations of our knowledge that we have already pointed out and in the light of the apparent complexity and variability of these diseases in man. For the two syndromes we will consider, Parkinson’s disease and Huntington’s disease, it will be obvious that we are comparing activity of neurons that are precisely localized with diseases that may be affecting brain areas outside the basal ganglia. For example, Parkinson’s disease is comprised of different subtypes and frequently involves brain areas outside the basal ganglia, including the locus coeruleus and the cerebral cortex (Greenfield and Bosanquet, 1953). Our hope, however, is that knowledge of the underlying neuronal mechanisms might make the symptoms of the disease more informative.

Our approach to the comparison of man and monkey rests on our observation that the nigro-collicular connection probably has two functions: first, to suppress saccade-related colliculus cells tonically, thereby preventing irrelevant visual information from activating the saccade generator; second, to remove the tonic inhibition thereby permitting initiation of a saccade. Diseases could disrupt the nigro-collicular connection by acting in at least four different ways: (1) insufficient nigro-collicular tonic inhibition, (2) overactive nigro-collicular tonic inhibition, (3) insufficient phasic removal of the nigro-collicular inhibition, (4) uncontrolled or excessive phasic removal of the nigro-collicular inhibition. We have already described in the pharmacological studies in monkeys some of these pathological states (Hikosaka and Wurtz, 1985a,b).

Patients with Parkinson’s disease show an impaired ability to initiate and execute voluntary movements. In addition to disorders of skeletal movements, the disease is accompanied by several different types of eye movement abnormality. Some, but not all, Parkinson’s patients show hypometric, slow saccades with somewhat lengthened latencies (Corin et al., 1972; De Jong and Melvill Jones, 1971; Melvill Jones and Defong, 1971; Shiba-saki et al., 1979; Shimizu et al., 1981; Teravainen and Calne, 1980a,b, White et al., 1983). These symptoms are those that would be predicted to result from an overactive nigro-collicular tonic inhibition (state 2) and the insufficiency of its removal (state 3). Both are related to an increase in inhibition of the SNr on the superior colliculus.

Although Parkinson’s disease has its primary pathological focus in the pars compacta, not the pars reticulata, pathological change in the compac-ta must indirectly alter the SNr and thus this output pathway from the basal ganglia. The dopaminergic fibers arising from the pars compacta, which are thought to be altered in Parkinson’s disease, could act on the pars reticulata in at least two ways. One would be by the action of the pars compacta on the striatum through the axo-dendritic connections of dopaminergic fibers on GABAergic striatal output cells (Kitai, 1976; Pickel et al., 1981). One possibility in Parkinson’s disease is that because of the lack of dopaminergic influence on the caudate cells, these cells have lost their phasic increase in activity.
at the time of saccades, the SNr cells consequently have no pause in inhibition, and they continue to inhibit superior colliculus cells even during saccades. The other possible effect of the compacta would be directly from the dendro-dendritic connections of the compacta dopaminergic cells onto the GABAergic pars reticulata cells (Cuvello and Iversen, 1978; Llinas et al., 1984). In this case the presumed overaction of the nigro-collicular connection might result from a reduction of the modulatory and inhibitory influence of dopamine on GABAergic cells (Waszczak et al., 1984).

Eye movement disorders in Parkinson's disease are conditional in nature. While deficits in saccades to visual targets are relatively slight, Parkinson's patients tend not to make saccades by anticipating the appearance of a target based on internal memory (Bronstein and Kennard, 1983). Such saccades, when made, are hypometric and slower compared with those of normal subjects (Carl and Wurtz, 1985). These results are compatible with those of the pharmacological experiments in which saccades to remembered targets were more affected than saccades to visual targets (Hikosaka and Wurtz, 1985a,b). Flowers (1978) has demonstrated a similar lack of prediction of Parkinson's patients in initiating skeletal movements. The similarity of these results in the skeletal and the oculomotor systems may indicate that this predictive function is critically related to the basal ganglia.

Huntington's disease is a hereditary disease characterized by irregular movements, disturbance of speech, and dementia. Deficits in oculomotor control include difficulty in suppressing saccades to novel stimuli and the presence of saccadic 'square-wave jerks' (Leigh et al., 1983; Bollen et al., 1986). This may correspond to one of the dysfunctions of the nigro-collicular connection, namely insufficient tonic inhibition (state 1), that has been mimicked by the injection of muscimol in the SNr or bicuculline in the superior colliculus. In fact, the pharmacological square-wave jerks in monkeys and those in man are remarkably similar. This interpretation of the square-wave jerk indicates a decrease in tonic inhibition, the opposite of our suggested interpretation of Parkinson's disease.

This suggestion of increased inhibition in Parkinson's disease and decreased inhibition in Huntington's disease is also a paradox because of other symptoms in patients with these diseases. Saccades of Huntington's patients are slow and hypometric (Avanzini et al., 1979; Bollen et al., 1986; Leigh et al., 1983; Starr, 1967). They have difficulty in initiating saccades, which is most evident when a patient is asked to look in a particular direction rather than at a specific visual target (Leigh et al., 1983). Both are consistent with increased inhibition. On the other hand, in Parkinson's disease, square-wave jerks have been reported in some patients (White et al., 1983) and this is consistent with decreased inhibition of the superior colliculus. These combinations of symptoms suggest that in different basal ganglia diseases the caudate-nigra-collicular system is disrupted in different ways or in different combinations. As we have already indicated, some of the deficits might also come from derangement of circuits outside the basal ganglia.

Our simple analysis based on increase or decrease in inhibition at the colliculus is by itself inadequate to explain the combination of symptoms. On the other hand, an understanding of the inhibitory mechanisms involved should sharpen the clinical evaluation of these patients with basal ganglia disease. For example, we do not know whether these patients show such opposing symptoms at the same time and for saccades to the same part of the visual field. In the light of current knowledge both are critical facts needed in understanding the neuronal mechanisms underlying these diseases of the basal ganglia.

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This chapter was completed in final form in April 1987