

CHAPTER 12

GABAergic output of the basal ganglia

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Abstract: Using GABAergic outputs from the SNr or GP_i, the basal ganglia exert inhibitory control over several motor areas in the brainstem which in turn control the central pattern generators for the basic motor repertoire including eye–head orientation, locomotion, mouth movements, and vocalization. These movements are by default kept suppressed by tonic rapid firing of SNr/GP_i neurons, but can be released by a selective removal of the tonic inhibition. Derangement of the SNr/GP_i outputs leads to either an inability to initiate movements (akinesia) or an inability to suppress movements (involuntary movements). Although the spatio-temporal patterns of individual movements are largely innate and fixed, it is essential for survival to select appropriate movements and arrange them in an appropriate order depending on the context, and this is what the basal ganglia presumably do. To achieve such a goal, however, the basal ganglia need to be trained to optimize their outputs with the aid of cortical inputs carrying sensorimotor and cognitive information and dopaminergic inputs carrying reward-related information. The basal ganglia output to the thalamus, which is particularly developed in primates, provides the basal ganglia with an advanced ability to organize behavior by including the motor skill mechanisms in which new movement patterns can be created by practice. To summarize, an essential function of the basal ganglia is to select, sort, and integrate innate movements and learned movements, together with cognitive and emotional mental operations, to achieve purposeful behaviors. Intricate hand–finger movements do not occur in isolation; they are always associated with appropriate motor sets, such as eye–head orientation and posture.

Keywords: substantia nigra pars reticulata; internal segment of globus pallidus; caudate nucleus; putamen; selection of behavior; saccadic eye movement; superior colliculus; memory-guided behavior; sequential procedure; reward; involuntary movement

Outputs of the basal ganglia

The output of the basal ganglia is issued largely (but not exclusively) from the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GP_i) (Carpenter, 1981). The output neurons in the SNr and GP_i share two important features: (1) they are GABAergic and inhibitory

(Uno and Yoshida, 1975; Di Chiara et al., 1979; Yoshida and Omata, 1979), and (2) they fire tonically and rapidly (DeLong and Georgopoulos, 1981). The tonic firing is present even in vitro slice preparations (Nakanishi et al., 1987). This means that the brain areas that receive inputs from the basal ganglia are, by default, under a strong tonic inhibition. This is very important when we consider the functions and dysfunctions of the basal ganglia.

However, a mere tonic inhibition would not be useful for controlling behavior; some mechanisms

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that modulate the level of the tonic inhibition would be necessary. In fact, the activity of SNr and GP_i neurons does change (decrease or increase) when the animal is alert and behaving (Hikosaka and Wurtz, 1983a; Anderson and Horak, 1985). Anatomical and electrophysiological studies have suggested that these changes in neuronal activity are caused by inputs from other basal ganglia nuclei. A decrease in SNr or GP_i neuronal activity may be caused by a direct input from the striatum (caudate nucleus and putamen) which is, again, GABAergic and inhibitory (Yoshida and Precht, 1971; Hikosaka et al., 1993a). An increase in SNr or GP_i neuronal activity may be caused by excitatory inputs from the subthalamic nucleus (STN) (Nakanishi et al., 1987; Robledo and Féger, 1990) or a decrease in inhibitory inputs from the external segment of the globus pallidus (GP_e) (Smith and Bolam, 1989).

These mechanisms give the basal ganglia a potential for controlling other brain areas by decreasing or increasing the inhibitions. An attractive hypothesis is that a major function of the basal ganglia is *the selection of appropriate behavior* (Hikosaka et al., 1993b; Mink, 1996; Nambu et al., 2002). Unwanted behaviors would be suppressed by maintaining or increasing the SNr/GP_i-induced inhibition while desired behaviors would be released by decreasing or removing the SNr/GP_i-induced inhibition. This hypothesis is consistent with movement disorders observed in patients with basal ganglia dysfunctions. A symptom commonly observed in basal ganglia patients is *involuntary movement*, which appears in various forms, such as tremor, dyskinesia, dystonia, chorea, athetosis, and ballism (Denny-Brown, 1968). Such involuntary movements could be caused by a reduction or interruption of the SNr/GP_i-induced inhibition. This is supported by single unit recording studies in such patients (Vitek et al., 1999; Starr et al., 2005) or experimental animal models (Wichmann et al., 1999; Raz et al., 2000). On the other hand, patients with basal ganglia dysfunction commonly have difficulty in initiating purposeful movements (akinesia) and, if initiated, the movements tend to be slow and small (hypokinesia). This type of movement disorder could be caused by an insufficient removal (or disinhibition) of the SNr/GP_i-induced inhibition (Burbaud et al., 1998).

The evidence based on clinical observations (as described above) for *the selection hypothesis* indicates a potential function of the basal ganglia, but not *the function* of the basal ganglia. In other words, it is still unclear whether the basal ganglia actually use the inhibition/disinhibition mechanisms to select purposeful behaviors (but see Aron and Poldrack, 2006). A real test of the selection hypothesis requires the recording of neuronal activity in the basal ganglia while the animal is performing purposeful behaviors.

In this chapter I will discuss the mechanisms and functions of the GABAergic output of the basal ganglia in relation to motor control. I will first discuss a series of studies using saccadic eye movement as a behavioral measure and then discuss other kinds of body movements. My discussion will be largely focused on the output of the SNr.

An example of basal ganglia-controlled functions — Saccadic eye movement

A big advantage of using saccadic eye movement as a behavioral measure is that its neuronal mechanisms have been studied extensively so that the basal ganglia mechanisms can be studied more or less independently from motor execution mechanisms. Let me first describe what aspects of saccadic eye movement are controlled by motor execution mechanisms in the brainstem, which is situated downstream to the basal ganglia.

Saccadic eye movement (or saccade) is an extremely fast and simultaneous rotation of the both eyes (typically 400°/s) (Becker, 1989). It is present in most vertebrates but is highly developed in primates (Easter, 1975). Its function is *orienting*, that is, to change the line of sight from one position to another (Grantyn et al., 2004). It occurs fairly frequently in primates, typically 2–3 times per second. Between saccades are the periods of visual fixation during which visual information on an object of interest is acquired through the fovea (the most sensitive part of the retina). Saccades must be fast because no or little visual information can be acquired while the eyes are rotating and consequently visual images are sweeping over the retina (Judge et al., 1980). Saccadic eye movements

are often accompanied by saccadic head movements (Guitton and Volle, 1987), which is more common among non-primate mammals (Fuller, 1985) and nonmammalian vertebrates (Du Lac and Knudsen, 1990).

The physical parameters of saccadic eye movement are controlled by the neuronal networks in the brainstem (Fuchs et al., 1985) and the cerebellum (Keller, 1989). For example, the fast rotation of the eyes is enabled by a high-frequency burst of spikes in *burst neurons* in the reticular formation, and this burst is enabled by the removal of tonic inhibition originating from *omnipause neurons* in the pontine raphe nucleus (Evinger et al., 1982). The burst and omnipause neurons are controlled by the superior colliculus (SC) (Raybourn and Keller, 1977), which receives direct inputs from the retina (Sparks, 1986). The SC (which may be called the optic tectum) plays a pivotal role in orienting behavior, which is crucial for survival (Goodale and Murison, 1975). Orienting of the eye-head-body is prerequisite for visually capturing an object (through the

fovea) and/or physically capturing the object (using the mouth, hand, or other body parts). In the SC are spatial maps for visual, auditory, and somatosensory information, and these sensory maps are in register with a motor map for orienting (Meredith et al., 1992). This organization serves a basic mechanism of behavioral orienting such that an object of interest, detected as one (or more than one) of the sensory information, is mapped onto a unique location in the SC, which then is converted to a vector (direction and magnitude) of eye and/or head movement (Sparks, 1986).

The involvement of the basal ganglia in the behavioral orienting was first suggested by the discovery of the efferent connection of the SNr to the SC (Rinvik et al., 1976; Jayaraman et al., 1977; Faull and Mehler, 1978; Graybiel, 1978; Vincent et al., 1978) (Fig. 1(B)). The discovery provided a good opportunity to study the function of the basal ganglia because the neuronal mechanisms downstream to the SC had already been understood to a great degree, as described above. Other

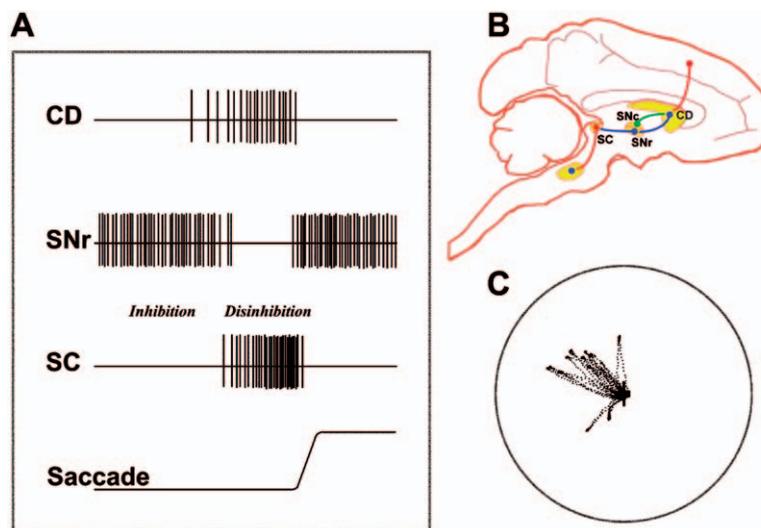


Fig. 1. Basal ganglia mechanism for control of saccadic eye movement. (A) A cardinal saccade mechanism in the basal ganglia. The SC is normally inhibited by rapid firing of GABAergic neurons in the SNr. The tonic inhibition can be interrupted by GABAergic inputs from the caudate nucleus. This disinhibition, together with excitatory cortical inputs, allows SC neurons to fire in burst, which leads to a saccade to a contralateral location. (B) Simplified neural circuits in the basal ganglia for control of saccadic eye movement in a parasagittal view of the macaque brain. Red, blue, green lines indicate excitatory, inhibitory, and modulatory connections. (C) Involuntary eye movement of a monkey after muscimol injection into right SNr, shown as trajectories of saccades during 2 s fixation periods. The monkey was unable to keep fixating at the central spot of light. Adapted with permission from (Hikosaka and Wurtz, 1985b).

efferent connections of the basal ganglia are either far more complex (as seen in the connections to the thalamus) or much less studied (as seen in the connections to brainstem areas other than the SC). Reinforcing the importance of the SNr–SC connection is the hypothesis stating that this connection is phylogenetically the best preserved one among the basal ganglia efferents (Marin et al., 1998; Reiner et al., 1998). This suggests that the essential or primary functions of the basal ganglia can be discerned by studying the SNr–SC connection in relation to saccadic eye movement.

Single unit recordings from the SNr in monkeys (Hikosaka and Wurtz, 1983a, b, c, d) and cats (Joseph and Boussaoud, 1985) performing saccade tasks provided firm evidence for the oculomotor role of the basal ganglia. In the following section I will summarize the results obtained in a series of studies on trained monkeys. Neurons related to saccadic eye movement were found mainly in the dorsolateral part of the SNr (Hikosaka and Wurtz, 1983a). Their typical response is a pause in firing in relation to events related to the preparation of saccades (Fig. 1(A)). The pause may occur as a visual response to a spot of light to which the monkey makes a saccade, as a pre-saccadic response, or as a sustained response during a delay period before the saccade (Hikosaka and Wurtz, 1983b, c). Most SNr neurons have response fields, usually centered in the contralateral hemifield, such that saccades into the response field are associated with stronger responses. Some SNr neurons increased firing in relation to saccades (Handel and Glimcher, 1999; Sato and Hikosaka, 2002).

Many of the saccade-related SNr neurons were activated antidromically by stimulating the intermediate layer of the SC where saccadic burst neurons are concentrated (Hikosaka and Wurtz, 1983d). This result suggested that the saccade-related SNr neurons have synaptic connections with saccade-related neurons in the SC, which was confirmed by anatomical studies (May and Hall, 1984; Karabelas and Moschovakis, 1985; Williams and Faull, 1988). There was a mirror-image relationship in activity between the antidromically activated SNr neurons and SC neurons recorded at the stimulation sites: the SNr neurons decrease firing while the SC neurons increase firing at similar time

periods during the preparation of saccades with similar directions and amplitudes (Fig. 1(A)). This result is consistent with the fact that the SNr–SC connection is inhibitory (Vincent et al., 1978; Chevalier et al., 1981).

These results support the *selection* function of the basal ganglia. Saccade-related SNr neurons are highly active, exerting a strong inhibition on saccade-related SC neurons, unless the saccade to a particular location is planned or executed. It is as if a gate were closed for the saccade. In fact, saccade burst neurons in the SC are inactive, rarely emitting spikes unless a saccade is about to be executed. Such quiescence may be maintained by the SNr–SC tonic inhibition. On the other hand, once SNr neurons stop firing, the strong inhibition would be removed at once, giving a strong drive for SC neurons to fire. It is as if the gate were opened.

A more straightforward demonstration of the SNr–SC gating function was obtained by the experimental blockade of the SNr–SC inhibition. When a small amount of GABA_A antagonist, bicuculline, was injected in the saccade-related region of the SC, the monkey became unable to keep fixating on a visual stimulus and made saccades incessantly to the side contralateral to the injection site (Hikosaka and Wurtz, 1985a). A likely explanation of such involuntary saccades is that the GABAergic SNr–SC inhibition was blocked by the GABA antagonist. Alternatively, the involuntary saccade might have been induced by the blockade of the effects of GABAergic interneurons within the SC. A support for the first hypothesis was obtained by an injection of GABA_A agonist, muscimol, in the SNr, which induced similar involuntary saccades to the contralateral side (Hikosaka and Wurtz, 1985b) (Fig. 1(C)). Since SNr neurons express an extremely high concentration of GABA_A receptors (Fahn and Cote, 1968; Okada et al., 1971) reflecting abundant GABAergic inputs from the striatum (caudate nucleus and putamen) and the external segment of the GP_e (Smith and Bolam, 1991), the injected muscimol would bind to the GABA_A receptors and suppress the rapid and tonic firing. This chemical manipulation would effectively remove the SNr–SC inhibition. The fact that the monkey developed involuntary saccades indicates that the SC is under the influence of excitatory inputs which are capable

of triggering spike activity in SC saccadic neurons, which however can be prevented by the SNr–SC inhibition.

These experimental results provide an insight into the motor control mechanisms. The excitatory inputs to the SC, which are normally gated by the SNr–SC inhibition, arise from many brain areas including the cerebral cortex and the cerebellum (Hikosaka et al., 2000). Among the cerebral cortical areas are the frontal eye field (FEF) (Bruce and Goldberg, 1985), supplementary eye field (SEF) (Schlag and Schlag-Rey, 1987), and the lateral intraparietal area (LIP) (Barash et al., 1991). All of these cortical areas contain many neurons that fire before saccades, although there seem some differences in their relationship to behavioral context (Coe et al., 2002). These results suggest that there is not a single area in the brain that dictates the initiation of saccadic eye movement. Individual cerebral cortical areas (and cerebellar areas as well) can contribute to saccade initiation, but only partially, by sending excitatory signals to the SC.

Such parallel excitatory inputs to the SC alone would not be suitable for the selection of behavior. Once some of these excitatory inputs are turned on simultaneously, their effects would be added up and reach the threshold for firing in SC neurons. The outcome would be uncontrollable emission of saccadic motor outputs, as observed when the SNr–SC inhibition was blocked. The SNr–SC tonic inhibition is capable of preventing the excitatory inputs from triggering off spike activity in SC neurons, and this is a necessary condition for selection. Selection would then be done by a pause in activity of SNr neurons, which is caused by GABAergic inhibitory inputs from the caudate nucleus (Hikosaka et al., 1993a) (Fig. 1(A)).

Functions of basal ganglia GABAergic outputs

So far I have been describing a neural mechanism of behavioral selection. However, for the mechanism to be functional, it must be operated appropriately. One way to answer this question is to examine the behavioral context in which the mechanism is deployed. An experimental objective

would then be to examine whether the key neurons constituting the mechanism (in this case SNr neurons) change their activity selectively in that context. This is a difficult task because the experimenter has to create the particular context by training the animal using a particular task and then test the key neurons. Experiments using this approach have revealed at least three kinds of behavioral context in which the basal ganglia appear to deploy its selection mechanism: (1) memory-guided behavior, (2) sequential procedure, and (3) reward-oriented behavior.

The selection of memory-guided behavior by the basal ganglia was first suggested by the discovery of neurons in the SNr that pause (Hikosaka and Wurtz, 1983c) and neurons in the caudate nucleus that burst (Hikosaka et al., 1989a) selectively or preferentially with memory-guided saccades, as opposed to visually guided saccades. These results suggest that the SNr–SC inhibition is removed more readily when saccades are planned to an invisible, but remembered, stimulus. The lack of this function should lead to a preferential impairment of memory-guided saccades. Indeed, patients of Parkinson's disease and Huntington's disease may have difficulty in making memory-guided saccades compared with visually guided saccades (Crawford et al., 1989; Nakamura et al., 1994).

The deficits in memory-guided saccades may be relevant to a phenomenon often observed in patients with basal ganglia dysfunctions: parkinsonian patients are able to move in response to sensory stimulation, but otherwise are unable to initiate a movement (Cooke et al., 1978; Glickstein and Stein, 1991; Azulay et al., 2002). For example, parkinsonian patients, who have great difficulties in walking on a flat plane floor, could initiate and keep walking if there are visible steps on the floor. Such a peculiar phenomenon is usually described as a selective impairment in internally guided behavior. However, the concept of internally guided behavior is rather obscure. Its nature may, at least partly, be memory-guided behavior.

The second context in which the basal ganglia may play an important role is sequential procedure. A goal-directed learned behavior is often composed of a fixed sequence of elementary movements. To drink a glass of juice, for example, you

first go to the refrigerator, open its door, find a bottle of orange juice, retrieve it, open its cap, and pour the content into a glass. The whole sequence is organized smoothly, each movement predicting a next movement. Many neurons are found in the basal ganglia, especially the caudate and putamen, which become active after one event until a next predicted event (Hikosaka et al., 1989b; Kermadi and Joseph, 1995; Miyachi et al., 1997; Meyer-Luehmann et al., 2002; Fujii and Graybiel, 2005), as if they linked one elementary behavior to another. Some studies have shown that patients with basal ganglia dysfunctions may have difficulties in executing such sequential and learned movements smoothly (Stern et al., 1983). Human functional imaging studies have revealed activation in the basal ganglia when the subject performs such sequential movement (Lehericy et al., 2005) as well as nonmovement tasks (Tinaz et al., 2006).

One important aspect of sequential procedure is that it is acquired through repeated practice, and once acquired, it becomes automatic or habitual (Hikosaka et al., 1995). Several lines of evidence suggest that the basal ganglia are necessary for acquisition and/or maintenance of such habitual and sequential behavior (Barnes et al., 2005; Yin and Knowlton, 2006). For example, a series of studies in which monkeys were trained to press buttons in a fixed order have shown that the anterior part of the striatum (caudate and putamen) is necessary for learning of new sequences whereas the middle part of the putamen is necessary for the execution of learned sequences (Miyachi et al., 1997; Miyachi et al., 2002). In this task, learning occurs in both eye movements and hand movements (Miyashita et al., 1996).

The third context, reward-oriented behavior, has been emphasized recently. A goal-directed sequential behavior is typically culminated with the attainment of reward. Many striatal (caudate and putamen) neurons exhibit tonic activity before the reward delivery (Hikosaka et al., 1989b; Schultz et al., 1992; Hollerman et al., 1998). Similar reward-related activation has been found in the human basal ganglia (Delgado et al., 2000; Knutson et al., 2000; O'Doherty et al., 2002). Visual or saccadic activity of neurons in the caudate (Kawagoe et al., 1998; Watanabe et al., 2003b) and the SNr

(Sato and Hikosaka, 2000) is strongly enhanced or depressed depending on whether the current trial will end with a big reward or a small reward. This was demonstrated using a saccade task in which the amount of reward delivered after a correct saccade is big for one direction, but small for the other directions; the task is called one-direction-reward task (1DR). The reward-dependent modulation of caudate neuronal activity is so strong that the neuron's response field can be changed completely depending on the rewarded location (Kawagoe et al., 1998). A group of caudate neurons exhibit sustained activity before a saccade depending on the rewarded location (Lauwereyns et al., 2002; Takikawa et al., 2002a). The reward-modulated activity of caudate neurons is transmitted to the SC (Ikeda and Hikosaka, 2003) through the SNr, leading to a biased tendency of saccades, namely, facilitation of saccades to the big-reward position (i.e., shorter latencies) and inhibition of saccades to the small-reward position (i.e., longer latencies) (Takikawa et al., 2002b; Watanabe et al., 2003a).

Further experiments suggest that the reward-dependent modulation of caudate neuronal activity is, at least partly, caused by inputs from dopamine neurons. Schultz and colleagues have shown that dopamine neurons, which are located in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA), respond to unexpected reward or a sensory event that indicate the upcoming delivery of reward (Schultz, 1998, 2002). In the 1DR saccade task, dopamine neurons exhibit a short burst of spikes in response to the big-reward-indicating target and a decrease in spike activity in response to the small-reward-indicating targets, regardless of the direction of the big reward (Kawagoe et al., 2004). In other words, the visual-saccadic activity of most caudate neurons is enhanced when it is associated with a burst of dopamine release in the caudate, but is depressed when it is associated with a reduction of dopamine release (Hikosaka et al., 2006). The causal relationship of dopamine release in the caudate, activity of caudate projection neurons, and saccadic eye movement is suggested by an experiment in which dopamine D1 or D2 antagonist was injected in the caudate (Nakamura and Hikosaka, 2006). The reward-dependent modulation of saccade

latencies was attenuated by the injection of D1 antagonist, but enhanced by the D2 antagonist. This suggests that the reward-modulation of saccadic eye movement is caused by the changes in neuronal activity in the caudate which depends on the reward-dependent changes in dopaminergic inputs to caudate projection neurons (Hikosaka et al., 2006).

Note that such reward-dependent modulation is not unique to the basal ganglia. Neuronal activity in many areas in the cerebral cortex is modulated by expected reward in monkeys (Watanabe, 1996; Platt and Glimcher, 1999; Tremblay and Schultz, 2000; Kobayashi et al., 2002; Roesch and Olson, 2003; Sugrue et al., 2004; Amiez et al., 2006) and in humans (O'Doherty et al., 2001; Ramnani and Miall, 2003; McClure et al., 2004). For example, activity of neurons in the frontal eye field can be modulated strongly by expected reward or expected reward position, although the modulation is not so drastic as in the caudate (Ding and Hikosaka, 2006). Nonetheless, the evidence described above certainly indicates that the source of reward-oriented behavior is at least partly in the basal ganglia.

Basal ganglia GABAergic control of basic movements

So far I have been discussing the function of the basal ganglia in relation to the control of saccadic eye movement, which is mediated by the SNr-SC connection. It is then tempting to hypothesize that other kinds of body movements or behaviors may also be controlled directly by the basal ganglia. Noteworthy in this respect is the fact that the basal ganglia send their outputs to many areas in the midbrain and the brainstem, which contain neural mechanisms of specific motor behaviors. Although this idea may be found in a long-standing concept of the extrapyramidal motor system (Jung and Hassler, 1960), recent studies using more controlled paradigms have provided strong support for this hypothesis.

A powerful technique to study this issue is reversible blockade of neuronal activity, typically by injecting muscimol (GABA_A agonist) into localized areas within the SNr or GP_i (Hikosaka and Wurtz,

1983e). Since a great majority of basal ganglia output neurons in the SNr and GP_i are GABAergic and exhibit tonic rapid firing, the basal ganglia control of motor behaviors is likely to use the same mechanisms as used for the control of saccadic eye movement, namely, tonic inhibition and disinhibition. Injected muscimol would inhibit surrounding neurons in the SNr or GP_i, remove the tonic inhibition on the target structures, and release body movements or other behaviors that are controlled by the neurons in the target structures. For example, muscimol injections in the rat SNr induced a wide variety of body movements, including movements of the head, mouth, and upper and lower limbs in addition to saccadic eye movements (Sakamoto and Hikosaka, 1989). Subsequent studies have demonstrated that different subregions in the SNr or GP_i have control over different kinds of motor behaviors, as shown below (Fig. 2).

Locomotion and posture

It is known that the oscillatory pattern of locomotion is generated by intricately connected

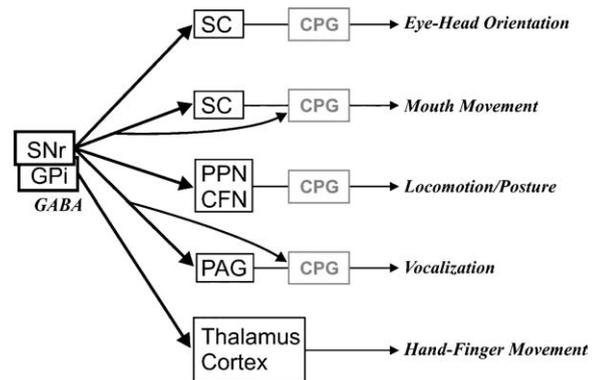


Fig. 2. Body movements controlled by the basal ganglia. With their projections to the brainstem motor areas and thalamus, GABAergic neurons in the SNr and GP_i keep suppressing various body movements but remove the suppression selectively to fulfill biological and motivational needs. The output of each brainstem motor area is mediated by a central pattern generator (CPG) located in the reticular formation or the spinal cord where a fixed spatiotemporal pattern of specific movement is generated. SC: superior colliculus; PPN: pedunculopontine nucleus; CFN: cuneiform nucleus; PAG: periaqueductal gray.

neurons in the spinal cord (Grillner, 1985). Such locomotor movements, together with an increase in muscle tone, are initiated by electrical or chemical stimulation of an area at the junction of the midbrain and the pons, which approximately corresponds to the cuneiform nucleus and is often called *midbrain locomotor region* or MLR (Grillner and Shik, 1973; Mori, 1987). In contrast, stimulation of the pedunculopontine nucleus (PPN), which is adjacent to the MLR, suppresses postural muscle tone (Takakusaki et al., 2003). The MLR- and PPN-mediated effects are mediated by their efferent pathways through the pontine and medullary reticular formation, and the effects remain even after being disconnected from the forebrain (i.e., decerebrate preparation) (Takakusaki et al., 2004a). Taken together, MLR and PPN play pivotal roles in locomotion and posture.

The role of the GABAergic outputs of the basal ganglia in the control of locomotion and posture was first suggested by Garcia-Rill (1986). It has been known that the mesopontine tegmentum, including the MLR and the PPN, receives a substantial amount of inputs from the basal ganglia, especially the SNr (Beckstead et al., 1979; Garcia-Rill et al., 1983; Spann and Grofova, 1991). Electrical stimulation of the SNr induces monosynaptic IPSPs in PPN neurons (Noda and Oka, 1986; Kang and Kitai, 1990). In a series of experiments, Takakusaki and colleagues demonstrated that the basal ganglia control locomotion and posture using the SNr–GABAergic output (Takakusaki et al., 2004a) (Fig. 2). They found that electrical stimulation at the lateral part of the SNr blocked the PPN-induced muscle tone suppression, whereas stimulation at the medial part of the SNr suppressed the MLR-induced locomotion (Takakusaki et al., 2003). The heterogeneous effects of SNr-stimulation suggest that the SNr is capable of controlling locomotion and posture using different channels depending on a given context.

A cardinal symptom of Parkinson's disease is gait disturbance in which the patients have difficulties in initiating or terminating walking (Azulay et al., 2002). It has been shown that the level of the GABAergic outputs of the basal ganglia is abnormally increased in Parkinson's patients (Miller and DeLong, 1987; DeLong, 1990; Filion and

Tremblay, 1991). The studies by Takakusaki and colleagues suggest that the gait disturbance of Parkinson's patients is caused by an abnormal increase in the SNr-induced inhibition of the MLR. On the other hand, muscle rigidity, which is characterized by excessive muscle tone, may be due to an abnormally increased inhibition of the PPN which otherwise would contribute to muscle relaxation. This pathological mechanism may also account for changes in muscle tone observed in other basal ganglia disorders. Dystonia, which is characterized by focal and involuntary changes in muscle tone, posture, or movements, may be caused by a reduction or derangement of the GABAergic outputs of the basal ganglia to the PPN (Starr et al., 2005). Hypotonia, which is associated with Huntington's chorea, may be caused by a decreased SNr–PPN inhibition. To summarize, these studies on the MLR and the PPN have provided a clear and straightforward view on the locomotor function of the basal ganglia.

Important issues remain to be solved, however. First, the experiments on the MLR and the PPN have been done using quadrupedal animals (cats and rats), and it is unknown whether the same mechanisms exist in bipedal humans. Second, it is unclear what drives or dictates the SNr-induced control of locomotion and posture. One possibility is that the nucleus accumbens (or the ventral striatum), which projects to the SNr (Lynd-Balta and Haber, 1994), controls locomotion (Brudzynski and Mogenson, 1985). On the other hand, the ventral striatum is now known to carry reward-related motivational signals in rodents (Nicola et al., 2004), monkeys (Schultz et al., 1992), and humans (Knutson et al., 2001; Pagnoni et al., 2002). These results together suggest that the ventral striatum, by sending signals to the SNr, controls reward-oriented locomotion. This scheme (ventral striatum–SNr–MLR/PPN) appears to parallel the caudate–SNr–SC mechanism, which controls reward-oriented saccadic eye movement. In fact, an essential part of reward-seeking behavior is to approach the place where reward may be available. The basal ganglia may control the two elements of reward-seeking behavior, orienting and locomotion, using separate mechanisms (Goodale and Murison, 1975).

A sustained decrease (or loss) of muscle tone occurs during rapid eye movement (REM) sleep. Several lines of evidence suggest that the PPN and surrounding regions are responsible for the REM-associated muscle atonia (Rye, 1997; Datta and Siwek, 2002). Using decerebrate cats Takakusaki and colleagues created the behavioral state that mimics REM (with atonia) by stimulating the PPN, and showed that additional stimulation at the lateral part of the SNr abolished the PPN-induced REM (Takakusaki et al., 2004b). This study suggested that the SNr is capable of controlling REM with its GABAergic connection to the PPN. This mechanism may be involved in sleep disorders that are often observed in parkinsonian patients (Larsen and Tandberg, 2001).

Mouth movements

The central pattern generator for rhythmical mouth movements is located in the medial part of the medullary reticular formation (Chandler and Tal, 1986; Nozaki et al., 1986). This area contains premotor interneurons that are involved in various types of mouth movements (Nozaki et al., 1993), and is directly controlled by the mouth area of the motor cortex (Nozaki et al., 1986). That the basal ganglia also control mouth movements has been suggested by electrical and chemical stimulation studies (Nakamura et al., 1990). Using chronically decorticated rats (Inchul et al., 2005) found that electrical stimulation at the ventral part of the SNr induced rhythmic activity in orofacial muscles and that an injection of GABA in the same region induced sustained elevation of muscle activity. These effects could be mediated by the SNr–GABAergic connection to the medullary reticular formation (Von Krosigk and Smith, 1991; Yasui et al., 1992). Another line of evidence suggests that mouth movements are mediated by the SNr–SC connection (Fig. 2): Apomorphine-induced mouth movements are suppressed by ablation of the SC (Chandler and Goldberg, 1984), mouth movements can be evoked by GABA_A receptor blockade in the lateral deep layer of the SC (Adachi et al., 2003), and the lateral SC is thought to be critical for mouth movements (biting and licking)

directed at noxious stimuli applied to the limb (Wang and Redgrave, 1997). The mouth movement region in the SC may extend to the mesencephalic reticular formation (Hashimoto et al., 1989), which may also receive inputs from the SNr (Beckstead, 1983; Yasui et al., 1994). The basal ganglia control of mouth movements is further supported by neuronal activity accompanied by natural mouth movements found in the SNr (Mora et al., 1977; Joseph et al., 1985; Nishino et al., 1985) and other basal ganglia nuclei (Mittler et al., 1994; Masuda et al., 2001).

Mouth movements include biting, licking, chewing, and swallowing, which constitute a basic means of food and liquid intake. Following orienting movements (including saccadic eye movement) and locomotion (discussed above), mouth movements would complete reward-seeking behavior. These considerations suggest that an essential function of the basal ganglia is to control reward-seeking behavior by organizing and sequencing multiple body movements.

Vocalization

Vocalization, which involves mouth movements, may also be controlled by the basal ganglia. A large body of evidence comes from clinical observations of basal ganglia patients. Vocalization is weak in Parkinson's patients (Goberman and Elmer, 2005). Dysarthria is common among patients with corticobasal degeneration (Ozsancak et al., 2000). Patients with Tourette syndrome may burst out with grunts or obscene words, in addition to abrupt and ritualistic movements of various body parts. Imaging and postmortem studies have shown that the size of the basal ganglia nuclei is abnormally small in Tourette patients (Leckman et al., 1991; Peterson et al., 1993; Singer et al., 1993). Dopamine antagonists or agonists may be used for treatment, suggesting an involvement of the basal ganglia. A recent postmortem study indicated that the number of parvalbumin-positive GABAergic neurons is abnormal in the GP_i and the caudate (Kalanithi et al., 2005).

Vocalization involves coordinated activity in respiratory, laryngeal, and orofacial muscle groups.

Similarly to orienting, locomotion, and mouth movements, vocalization is likely to be controlled by a central pattern generator which is located in the nucleus retroambiguus (Holstege, 1989; Zhang et al., 1995) or in the parvocellular reticular formation around the nucleus ambiguus (Kirzinger and Jürgens, 1991; Hage and Jürgens, 2006), or both. This vocal pattern generator is controlled by the periaqueductal gray (PAG) (Zhang et al., 1995), which is known to control vocalization (Jürgens and Pratt, 1979; Larson and Kistler, 1986; Zhang et al., 1994). The PAG is known to be innervated by the SNr (Hopkins and Niessen, 1976; Cebrian et al., 2005; Castellán-Baldan et al., 2006), and this might be responsible for the basal ganglia control of vocalization (Von Krosigk and Smith, 1991) (Fig. 2). However, there has been no study, to my knowledge, that tested this hypothesis.

The role of the basal ganglia in vocalization has been studied in relation to bird song. In the bird-brain is an area called X, which is equivalent to the striatum and the GP_i combined in mammals (Farries and Perkel, 2002). Area X contains a large number of GABAergic neurons, similarly to the SNr/GP_i and the striatum, and is essential for the bird to learn to sing species-specific songs. As in the mammalian striatum, inputs from the hyperstriatum (corresponding to the mammalian cerebral cortex) to neurons in area X are modulated presynaptically by dopamine (Ding et al., 2003) and undergo synaptic plasticity (LTP) in the presence of dopamine (Ding and Perkel, 2004). These studies on the role of the basal ganglia in bird song should motivate more research in the mammalian brain.

Similarly to orienting, locomotion, and mouth movements, vocalization is a basic motor behavior whose patterns are generated by distinct neural circuits in the brainstem. On the other hand, vocalization is used for expression of emotions and social communications (Gil-da-Costa et al., 2004; Poremba et al., 2004), which require complicated context-dependent selections. The basal ganglia mechanisms utilizing their GABAergic outputs to the brainstem vocalization centers may play important roles in such selections.

Hand-finger movements

A majority of basal ganglia outputs is directed to several nuclei in the thalamus including nucleus ventralis lateralis (VL), nucleus ventralis anterior (VA), nucleus centrum medianum (CM), nucleus parafascicularis (Pf), and nucleus medialis dorsalis (MD) (Graybiel and Ragsdale, 1979; Carpenter, 1981; Parent, 1990). These thalamic nuclei are mutually connected with different areas in the cerebral cortex (Colwell, 1975) and in addition project to the striatum (caudate and putamen) (Beckstead, 1984; Sadikot et al., 1992; McFarland and Haber, 2001). In both cases the information sent out of the basal ganglia may be returned to the basal ganglia forming loop circuits: cortex-striatum-SNr/GP_i-thalamus-cortex and striatum-SNr/GP_i-thalamus-striatum. A dominant hypothesis is that the loop circuits are parceled into several divisions, which correspond to different functions such as sensorimotor, oculomotor, cognitive, and limbic functions (Alexander et al., 1986). While the presence of such loop circuits is likely, it is unclear whether the different loop circuits are independent. An alternative hypothesis is that signals can be relayed from one functional loop to another like a spiral (Haber et al., 2000). The latter type of information processing may be advantageous in integrating different kinds of information (e.g., cognitive and emotional), which is required for purposeful behaviors. The general scheme of the basal ganglia outputs to the thalamus described above suggest that the basal ganglia are capable of contributing to almost all kinds of functions.

A prominent motor function that is likely to be controlled by the basal ganglia output to the thalamus, not their output to the brainstem structures, is motor skill (Fig. 2). Motor skills are likely to be controlled by the mechanisms located in the motor cortices, cerebellum, basal ganglia, or these areas combined (Hikosaka et al., 1999; Hikosaka et al., 2002), not by the central pattern generators located in the brainstem or spinal cord. A distinct feature of motor skills is that they are acquired through repeated practice, and many studies suggest that the basal ganglia are involved in the

learning process and possibly in the storage of the procedural skill memory as well (Miyachi et al., 1997; Hikosaka et al., 1999; Miyachi et al., 2002; Lehericy et al., 2005). These results suggest that, among the different lines of basal ganglia outputs, the output to the thalamus is likely to be involved in motor skills. With its output to the thalamus the GP_i is deeply involved in motor skills, whereas the SNr is preferentially involved in cognitive or emotive functions (Sidibe et al., 2002). An outstanding example of motor skills is skilled hand–finger movement, which is particularly developed in primates (Wiesendanger, 1999). Another motor skill largely unique to humans is speech, which seems to require the intact basal ganglia (Damasio, 1983; Ullman, 2001).

Pathological mechanisms of GABAergic outputs of the basal ganglia

I suggested previously that the basal ganglia GABAergic output acts as a gate for motor signals such that there should be no motor output as long as the gate is closed. For this gating function to work properly, the level of the GABAergic output must, by default, be maintained at a steady level. A subtle change in this mechanism may cause serious problems in motor behavior. An example is found in Parkinson's disease. It has repeatedly been shown that the average level of the basal ganglia GABAergic output is higher in Parkinson's patients compared with control subjects. The enhanced GABAergic output would excessively suppress the target areas including the SC, MLR, PPN, thalamo-cortical circuits, and possibly mouth movement and vocalization centers, leading to akinesia or hypokinesia. On the other hand, dyskinesias induced by L-DOPA (dopamine precursor) or apomorphine (dopamine agonist) are associated with a reduction of the basal ganglia GABAergic outputs (Nevet et al., 2004). The depressed GABAergic output would be insufficient to suppress the motor centers mentioned above, which leads to excessive body movements, dyskinesia.

Further experiments support these conclusions. If the GABAergic output is reduced by injecting

muscimol (GABA_A agonist) in the SNr of MPTP-induced parkinsonian monkeys, their body movements are improved (Wichmann et al., 2001). In normal monkeys injections of muscimol (GABA agonist) in the GP_i, which should reduce the GABA output, induces choreiform movements, while injections of bicuculline (GABA_A antagonist) in the GP_i, which should block incoming GABA-induced inhibitions, induced hypokinesia (Burbaud et al., 1998). Bergmann and colleagues have also shown that the GABAergic output is not stable but fluctuates in an oscillatory manner in MPTP-induced parkinsonian monkeys, but not in control monkeys (Bar-Gad et al., 2004). This should lead to oscillatory firing of motor neurons in the above areas, which may induce tremor or other involuntary movements.

Some mechanisms have been suggested for the deranged GABAergic output of the basal ganglia. GABAergic neurons in the SNr/GP_i are highly sensitive to GABAergic inputs that arise from the GP_e or caudate/putamen. It has been shown that the level of GABAergic outputs of the GP_e is lower in Parkinson's patients, which might be a cause of an increase in GABAergic outputs of the SNr/GP_i. However, this would not be an ultimate explanation because the primary cause of Parkinson's disease is a loss of dopamine neurons in the SNc. Some studies have shown that dopamine released or delivered in the SNr can cause short-term and long-term changes in the activity of GABAergic output neurons (Waszczak and Walters, 1986; Miyazaki and Lacey, 1998; Trevitt et al., 2001) which may be paralleled by dyskinesia (Vila et al., 1996; Katz et al., 2005).

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