C. Kennard & R.J. Leigh (Eds.)
Progress in Brain Research, Vol. 171
ISSN 0079-6123

CHAPTER 2.1

Neural circuits for triggering saccades in the brainstem

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Abstract: Here we review the functional anatomy of brainstem circuits important for triggering saccades. Whereas the rostral part of the superior colliculus (SC) is considered to be involved in visual fixation, the caudal part of the SC plays an important role in generation of saccades. We determined the neural connections from the rostral and caudal parts of the SC to inhibitory burst neurons (IBNs) and omnipause neurons (OPNs) in the nucleus raphe interpositus. To reveal the neural mechanisms of triggering saccadic eye movements, we analysed the effects of stimulation of the SC on intracellular potentials recorded from IBNs and OPNs in anaesthetized cats. Our studies show that IBNs receive monosynaptic excitation from the contralateral caudal SC, and disynaptic inhibition from the ipsilateral caudal SC, via contralateral IBNs. Further, IBNs receive disynaptic inhibition from the rostral part of the SC, on either side, via OPNs. Intracellular recording revealed that OPNs receive excitation from the rostral parts of the bilateral SCs, and disynaptic inhibition from the caudal SC mainly via IBNs. The neural connections determined in this study are consistent with the notion that the ''fixation zone'' is localized in the rostral SC, and suggest that IBNs, which receive monosynaptic excitation from the caudal ''saccade zone,'' may inhibit tonic activity of OPNs and thereby trigger saccades.

Keywords: superior colliculus; inhibitory burst neuron (IBN); omnipause neuron (OPN); abducens motoneuron; fixation neuron; saccade

Introduction

Jean Büttner-Ennever has done much to clarify brainstem anatomy concerned with saccade generation by using innovative tracer and histochemical techniques. Here we summarize our contribution, which consists of studies of the functional anatomy of saccades in the anaesthetized cat. The superior colliculus (SC) contains a motor map that reflects direction and size of saccades (Robinson, 1972; Guitton et al., 1980; McIlwain, 1986). On this map, the rostral SC reflects the foveal region of the retina, and contains neurons that discharge continuously during visual fixation (Munoz and Guitton, 1989, 1991; Munoz and Wurtz, 1993). Conversely, the caudal SC contains movement neurons that start firing before the onset of saccadic eye movement (Munoz and Wurtz, 1995; Stanford et al., 1996). Stimulation of the caudal SC evokes saccadic eye movements to the contralateral side (Robinson, 1972), whereas stimulation of the rostral SC suppresses generation

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DOI: 10.1016/S0079-6123(08)00611-0

of saccadic eye movements (Paré and Guitton, 1994; Gandhi and Keller, 1999). Therefore, currently, it is often accepted that there are two regions in the SC that have different functions; the "saccade zone" that encodes saccade generation, and the "fixation zone" that encodes visual fixation. More recently, the idea of functional independence of the rostral "fixation zone" has been challenged, since microstimulation of the SC indicated that the saccade size was continuously represented from the caudal to the rostral SC (Gandhi and Keller, 1999). If two different systems of reciprocal functions, i.e., maintaining fixation vs. generating saccades do exist in the rostral and caudal SC, respectively, then the respective parts of the SC should have different neural connections with abducens motoneurons (MNs), inhibitory burst neurons (IBNs), and omnipause neurons (OPNs) in the saccade generator of the brainstem. However, the projections from the rostral and caudal parts of the SC to brainstem saccade generators require clarification.

The OPNs are located in the nucleus raphe interpositus (Büttner-Ennever et al., 1988). There are two important questions concerning the role of OPN in the generation of saccades. First, which excitatory neurons maintain sustained activity of OPNs during steady visual fixation? Second, which inhibitory neurons suppress activity of OPNs so that saccades can be initiated and break fixation? Despite the numerous studies, the neural circuits for triggering saccades by inhibiting OPN activity still remain controversial.

To understand the neural mechanism of generation of saccades and their suppression during visual fixation, we investigated the neural projections from the rostral and caudal SC to IBNs and OPNs in anaesthetized cats by recording intracellular potentials from them. We found different input patterns from the rostral vs. caudal SC to IBNs and OPNs. Thus, IBNs receive monosynaptic excitation and disynaptic inhibition from the caudal SC on the contralateral and ipsilateral side, respectively, and disynaptic inhibition from the bilateral rostral SCs. Most OPNs receive monosynaptic excitation from the rostral SCs and disynaptic inhibition from the caudal SCs. This disynaptic inhibition to OPNs is mediated by IBNs. Possible roles of IBNs in triggering of saccades by actively inhibiting the tonic activity of OPNs will be discussed.

Identification of IBNs and synaptic inputs from the SC to IBNs

To analyse projections from the SCs to IBNs, we searched for neurons in the IBN region about 0.8 mm lateral to the midline. We used the following criteria for identifying penetrated neurons as IBNs; (1) location of a cell in the pontomedullary junction (IBN region), (2) antidromic activation from the contralateral abducens nucleus, (3) monosynaptic excitation from the contralateral caudal SC, and (4) disynaptic inhibition from the ipsilateral caudal SC. To confirm the recorded neurons as IBNs, we injected horseradish peroxidase (HRP) into cell bodies or proximal axons of presumed IBNs that satisfied the criteria listed above, and examined the morphologies of the penetrated cells at the early stages of this series of experiments. The stained cells had morphological features that were similar to electrophysiologically identified IBNs (Yoshida et al., 1982; Strassman et al., 1986).

To investigate the properties of synaptic inputs from the rostral and caudal parts of the SC to IBNs, we recorded intracellular potentials from IBNs and examined effects of stimulation at four rostrocaudal sites in each SC (Fig. 1B). Stimulation of the rostral and caudal parts of the ipsilateral SC evoked inhibitory postsynaptic potentials (IPSPs) in an IBN (Fig. 1B1–4), whereas stimulation of the contralateral SC evoked excitatory postsynaptic potentials (EPSPs) in the same cell (Fig. 1B6–8). The IPSPs and EPSPs usually increased as the stimulation sites moved caudally in the SC. In addition, the most rostral site in the contralateral SC was different from the more caudal sites in that stimulation of the most rostral site evoked IPSPs in the IBN (Fig. 1B5).

Next, we compared the patterns of collicular inputs to IBNs (Sugiuchi et al., 2005) with those to abducens MNs (Izawa et al., 1999). Stimulation of any site of the ipsilateral SC evoked disynaptic IPSPs in abducens MNs (Fig. 1C1–4). This pattern was similar to the pattern described above in IBNs.

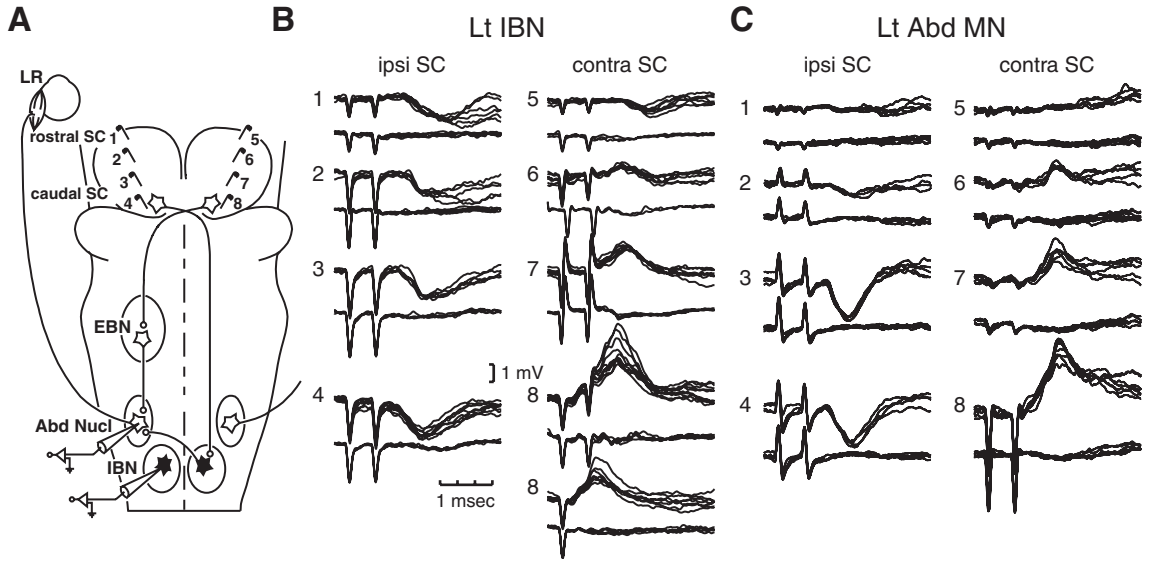

Fig. 1. Comparison of synaptic inputs from the superior colliculi (SCs) on both sides to an inhibitory burst neuron (IBN) (B) and an abducens motoneuron (MN) (C). (A) Experimental setup. LR, lateral rectus muscle; EBN, excitatory burst neuron. (B) Postsynaptic potentials (PSPs) evoked in a left IBN by stimulation of the ipsilateral (1–4) and contralateral SC (5–8) at 500 μA. (C) PSPs evoked in a left abducens motoneuron by stimulation of the ipsilateral (1–4) and the contralateral SC (5–8) at 500 μA. Calibration for (B) applies also to (C). (Adapted with permission from Sugiuchi et al., 2005.)

However, abducens MNs did not usually receive inhibition from the most rostral SC, whereas IBNs always received disynaptic inhibition from the most rostral SC. Stimulation of the contralateral SC evoked excitation in abducens MNs and in IBNs, but the excitation was disynaptic in abducens MNs (Fig. 1C6–8) and monosynaptic in IBNs. Furthermore, stimulation of the most rostral part of the contralateral SC always evoked disynaptic inhibition in IBNs (Fig. 1B5), whereas it never evoked inhibition in abducens MNs (Fig. 1C5). This last finding is the most important difference of the synaptic input pattern between IBNs and abducens MNs.

Pathways from the SC to IBNs

To identify the pathways from SC to IBNs, we made a transverse section in the *right* medial longitudinal fasciculus at a level, about 2 mm rostral to the rostral end of the abducens nucleus, and interrupted the tectoreticular tract connecting between the SC and the OPN region (Fig. 2A). Following sectioning, inhibition from the left rostral and caudal SC disappeared in a left IBN (Fig. 2Bb), but inhibition from the right rostral SC (Fig. 2Bd) remained unaffected in the same IBN. Moreover, stimulation of the caudal part of the left SC did not evoke monosynaptic excitation in a right IBN (Fig. 2Cb), and disynaptic IPSPs evoked by left rostral SC stimulation also disappeared in the same IBN (not shown). However, stimulation of the right rostral SC (Fig. 2Cd) and the right caudal SC (not shown) evoked disynaptic IPSPs in a right IBNs, similar to the control, indicating that the inhibition from the ipsilateral SC was not influenced by sectioning the tectoreticular axons on the same side as the IBNs. It follows that monosynaptic excitation and disynaptic inhibition from the contralateral SC to IBNs were most likely mediated by tectoreticular axons on the same side as the IBNs (Grantyn and Grantyn, 1982), and inhibitory interneurons that mediate this disynaptic inhibitory input were most likely to be located caudal to the level of the section. In contrast, disynaptic inhibition from the ipsilateral SC to IBNs was likely to be mediated by tectoreticular axons on the side opposite to the IBNs.

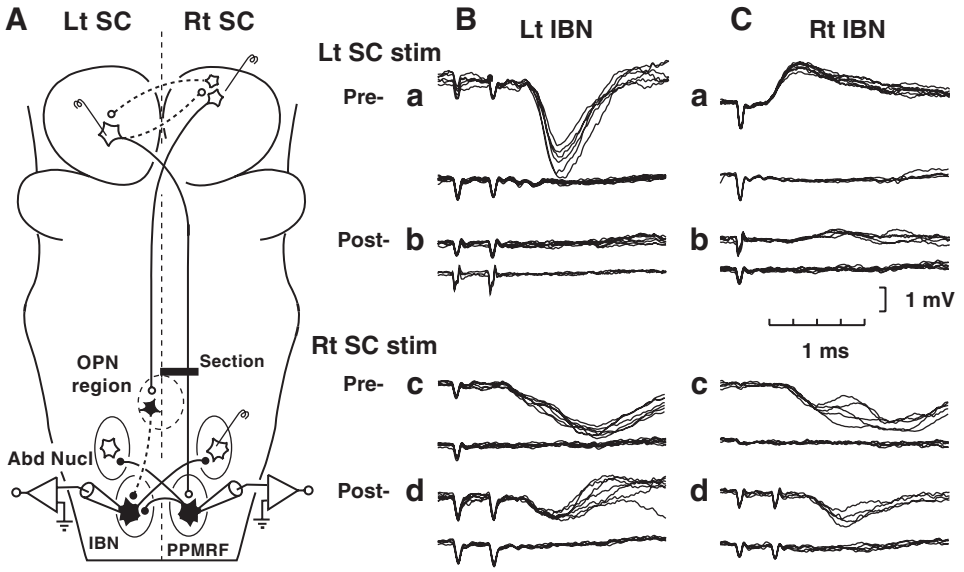

Fig. 2. Effects of the sectioning of tectoreticular axons (thick horizontal bar in A) on the right on SC-evoked PSPs in left (B) and right (C) IBNs. (A) Schematic diagram of the experimental setup. (B–C) Intracellular records from IBNs before (a, c) and after the sectioning (b, d). Note that inhibition from the right rostral SC remained in a left IBN (Bd) and a right IBN (Cd) after the sectioning of the right tectoreticular tract. This finding indicates that the inhibition from the right rostral SC to the left IBN is not due to collicular commissural activation (dotted axons in the SC) of tectoreticular neurons in the left SC. (Adapted with permission from Takahashi et al., 2005.)

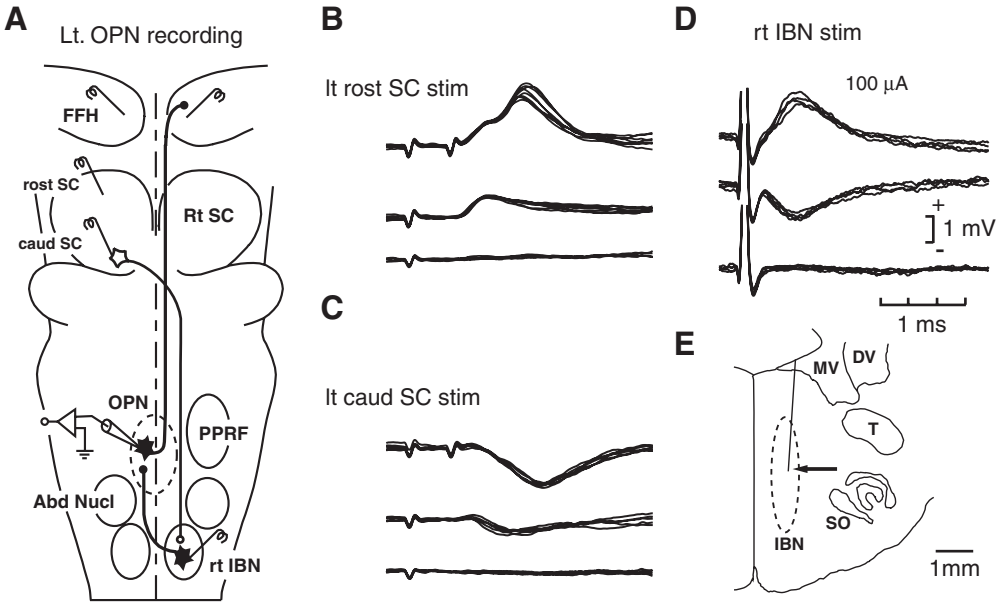

Fig. 3. Synaptic inputs from the SC (B–C) and the IBN region (D–E) to left omnipause neurons (OPNs). (A) Experimental setup. (B–C) EPSPs evoked by stimulation of the left rostral SC (B), and IPSPs evoked by stimulation of the left caudal SC in a left OPN (C). Upper, middle and lower traces; double and single stimulation and field potentials, respectively. (D) Monosynaptic IPSPs (middle traces) and reversed IPSPs after Cl^- injection (upper traces) evoked by stimulation of the right IBN region (arrow in E) in another left OPN. MV, DV, T and SO; medial and descending vestibular nucleus, trigeminal and superior olive nucleus, respectively.

As the stimulation sites in the SC were made more caudally, monosynaptic excitation in the contralateral IBNs increased, and disynaptic inhibition in ipsilateral IBNs and abducens MNs increased. These findings suggest that inhibition in IBNs from the ipsilateral caudal SC might be mediated by contralateral IBNs. To explore further this possibility, we analysed responses in IBNs evoked by stimulation of the contralateral IBN region. Stimulation of the contralateral IBN region evoked IPSPs, with latencies ranging from 0.7 to 1.8 ms. This latter finding showed that contralateral IBNs exerted monosynaptic inhibition on IBNs. We then confirmed that contralateral IBNs mediate disynaptic inhibition from the ipsilateral caudal SC to IBNs, by showing that the monosynaptic inhibition evoked from the contralateral IBN region was facilitated by preconditioning stimulation of the ipsilateral caudal SC.

To confirm further that the inhibition from the ipsilateral caudal SC to IBNs is mediated by contralateral IBNs, we examined the effect of sectioning the midline between the bilateral IBN regions. After a middle section, stimulation of the rostral part of the contralateral SC evoked IPSPs in an IBN. On the other hand, ipsilateral stimulation of the caudal SC did not evoke IPSPs, whereas that of the rostral SC evoked disynaptic IPSPs in the same IBN (Sugiuchi et al., 2005). Taken together, these results confirmed that the disynaptic inhibition from the ipsilateral caudal SC to an IBN is conveyed via contralateral IBNs, and the disynaptic inhibition from the rostral SC on either side is conveyed to IBNs via inhibitory interneurons other than IBNs, most likely OPNs.

Synaptic inputs from the rostral and caudal SC to OPNs

To demonstrate directly that disynaptic inhibition from the rostral SC to IBNs is mediated by OPNs, we recorded intracellular potentials from OPNs (Fig. 3) (Takahashi et al., 2005). OPNs were identified by their antidromic responses to stimulation of the Forel's H area and/or the IBN region. We found that stimulation of the rostral SC evoked EPSPs in an OPN (Fig. 3B). Since OPNs are reported to project to IBNs (Ohgaki et al., 1987; Strassman et al., 1987), our finding indicates that IBNs receive disynaptic inhibition from the rostral SC via OPNs. In contrast, stimulation of the caudal SC evoked disynaptic IPSPs in the same OPN (Fig. 3C). As shown in abducens MNs (Fig. 2), these IPSPs were most probably mediated via contralateral IBNs, because stimulation of the caudal SC could not evoke IPSPs after a transverse lesion in the contralateral medial longitudinal fascicle just rostral to the OPN region. In fact, stimulation of the contralateral IBN region (Fig. 3E) evoked monosynaptic IPSPs with weak stimulus intensity in an OPN (Fig. 3D). Stimulation of the ipsilateral IBN region also induced monosynaptic IPSPs in IBNs. Since IBNs send their stem axons across the midline without giving rise to collaterals on the ipsilateral side (Sugiuchi et al., 2005), this ipsilateral inhibition might be caused by an axon

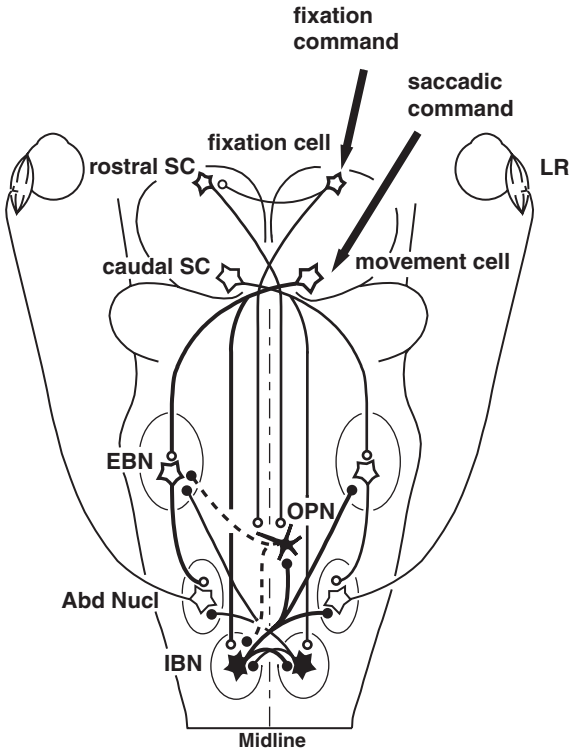

Fig. 4. Summary diagram of neural circuits from the rostral "fixation zone" and the caudal "saccade zone" of the SC to an IBN and an OPN for triggering saccades and visual fixation. Abd Nucl, abducens nucleus; LR, lateral rectus muscle.

reflex of IBN axons. Furthermore, preconditioning stimulation of the caudal SC facilitated the monosynaptic IPSPs evoked by stimulation of the contralateral IBN region (not shown). Therefore, these findings suggest that OPNs receive disynaptic inhibition via contralateral IBNs (Fig. 4).

Conclusions

Our studies have shown that IBNs receive monosynaptic excitation from the contralateral caudal SC, and disynaptic inhibition from the ipsilateral caudal SC via contralateral IBNs. In addition, IBNs receive disynaptic inhibition from the rostral parts of the bilateral SCs via inhibitory interneurons other than IBNs, most probably OPNs.

At saccade onset, SC neurons may activate contralateral excitatory burst neurons (EBNs) and IBNs, and these EBNs excite abducens MNs on the same side. The IBNs inhibit not only abducens MNs, but also IBNs and EBNs on the opposite side, since IBNs give rise to axon terminals in the contralateral abducens nucleus, the paramedian pontine reticular formation (PPRF) and the paramedian pontomedullary reticular formation (PPMRF) (Yoshida et al., 1982; Strassman et al., 1986; Sugiuchi et al., 2005). Therefore, this antagonistic inhibition at the supranuclear as well as at the motoneuronal level assures the suppression of saccade generation towards the opposite side.

Another important finding was that IBNs are disynaptically inhibited by the rostral parts of the bilateral SCs. Since a transverse section of tectoreticular fibres on the right side at the level just rostral to the OPN region eliminated IPSPs evoked by stimulation of the left rostral SC in right IBNs and left IBNs, intervening interneurons for these pathways must be OPNs. Fixation neurons in the rostral SC are antidromically activated by stimulation of the OPN region (Gandhi and Keller, 1997), and rostral SC stimulation activates OPNs (Paré and Guitton, 1994). In fact, intracellular recording from OPNs received monosynaptic excitation from the rostral parts of the bilateral SCs (Takahashi et al., 2005). Paré and Guitton (1994) reported that stimulation of the rostral SC suppresses the generation of saccades in both directions. However, rostral SC inhibition was usually stronger for ipsilateral IBNs than for contralateral IBNs. This result is consistent with the following anatomical data that tectoreticular neurons in the rostral pole of the SC terminate in the OPN region on the opposite site (Büttner-Ennever et al., 1999), and OPNs project mainly to the contralateral PPRF and the IBN region (Ohgaki et al., 1987).

Fixation neurons behaved as if their function was to actively maintain gaze on a target and prevent burst neurons from producing unwanted eye movements (Fuchs et al., 1985). Moreover, by ceasing to fire immediately before saccades away from a fixation target, fixation neurons may partly contribute to triggering of the saccade. Neurons in the "saccade zone" of the caudal SC may receive inputs from the cerebral cortex such as the frontal eye field (FEF) and the lateral intraparietal cortex, whereas fixation neurons in the "fixation zone" of the rostral SC most likely receive inputs from the "suppression area" of the FEF (Izawa et al., 2004). The present results suggest that fixation neurons in the bilateral rostral SCs suppress the initiation of saccades and maintain the direction of gaze by increasing the level of tonic inhibitory input to IBNs and EBNs via OPNs. On the other hand, these fixation neurons stop firing just before a saccade onset. Due to this disfacilitation, and also by active inhibition from the caudal "saccade zone" of the SC, OPNs may stop tonic firing to trigger saccades. Yoshida et al. (2002) showed that stimulation of the SC disynaptically inhibits OPNs. This disynaptic inhibition was considered to be mediated by inhibitory interneurons other than IBNs, most likely inhibitory long-lead burst neurons located in the PPRF (Kamogawa et al., 1996). However, the present result strongly suggests that IBNs are mainly responsible for active inhibition of OPNs at the onset of saccades (Fig. 4). Further study is required to provide anatomical evidence to support a strong projection of IBNs to OPNs.

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