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Inhibitory substantia nigra inputs to the pedunculopontine neurons

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Summary. Responses of 43 pedunculopontine area (PPN area) neurons to electrical stimulation of the substantia nigra (SN) were studied in anesthetized rats. An intracellular recording technique was used to demonstrate that SN stimulation evoked hyperpolarizing potentials, which were identified by intracellular injections as inhibitory postsynaptic potentials (IPSPs). These IPSPs were often followed by a rebound depolarization that originates several spike potentials. These IPSPs were characterized as monosynaptic, with latencies varying from 1.0 to 8.5 ms. Similar results were observed in some animals with chronic unilateral coronal lesion just rostral to subthalamic nucleus (STH), which severed the rostral afferents. PPN area neurons were also antidromically activated by SN stimulation. Two PPN area projection neurons were clearly identified. Mean latency of one group was 0.71 ms; mean latency of the second group was 5.16 ms. The morphological analysis of a neuron inhibited by SN stimulation and labeled with horseradish peroxidase (HRP) demonstrated that the soma was fusiform in shape, with the axon originating in the soma and collaterals and a large dendritic field extending in the ventrodorsalis direction. The results indicate that the PPN area is reciprocally connected with the SN, which elicits an inhibitory effect on PPN area neurons.

Key words: Pedunculopontine nucleus – Substantia nigra – Intracellular recording – IPSP – Antidromic activation – Rat

Introduction

The pedunculopontine tegmental nucleus (PPN) is located in the caudal mesencephalic tegmentum extending from the caudal border of the red nucleus to the parabrachial nucleus. As an extension of this nucleus, the pedunculopontine area (PPN area) may include the cuneiform (CNF) nucleus, the central tegmental field (CTF), the pontinotegmental field, and a group of cholinergic neurons in the vicinity of the superior cerebellar peduncle (Armstrong et al. 1983; Kimura et al. 1981; Satoh and Fibinger 1985a, b; Mesulam et al. 1984; Butcher et al. 1977). It has been demonstrated that this area receives direct descending projections from some components of the basal ganglia, i.e., the substantia nigra (SN), the entopeduncular nucleus, and the subthalamic nucleus (STH) (Beckstead et al. 1979; Nauta 1979; Moon-Edley and Graybiel 1983; Jackson and Crossman 1983; Kita and Kitai 1987). Electrophysiological studies demonstrate that SN inputs are inhibitory to the PPN area neurons in the cat in vivo and in the rat in vitro (Noda and Oka 1984, 1986; Kang and Kitai 1990). Moreover, extracellular studies reported reciprocal electrophysiological effects between the SN and PPN (Scarnati et al. 1987), and a disinhibitory action on PPN area neurons is produced by striatonigral pathway activation (Chevalier et al. 1985; Deniau and Chevalier 1985). These disinhibitory inputs will, in turn, activate PPN area neurons, but no further information could be obtained from extracellular recording techniques.

The purpose of this study was to identify and characterize the afferent inputs from the SN to the PPN area neurons in the rat using an intracellular recording technique in vivo. The neurons were labeled by intracellular injection of horseradish peroxidase (HRP) after recording electrophysiological data. The recording site and, in a particular case, the neuronal morphology through a serial reconstruction were analyzed on these experiments. These results demonstrate that inhibitory postsynaptic potential (IPSP) is the more prominent response evoked on PPN area neurons by SN stimulation in the rat. A strong rebound excitation was observed in some neurons, probably as a consequence and following the IPSP. In some neurons, SN stimulation evoked excitatory postsynaptic potentials (EPSPs), whereas in only three neurons hyper-

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polarizing potentials, probably the result of disfacilitation, were observed.

Material and methods

Twenty-five male Sprague-Dawley rats (weighing 250–350 g) were anesthetized with a combination of urethane (1.5–1.8 g/kg, i.p.) and ketamine hydrochloride (30 mg/kg, i.p.). Supplemental doses of ketamine hydrochloride were administered every 2 h throughout the experiment. These rats were mechanically ventilated with oxygen-enriched air and paralyzed with tubocurarine chloride (0.12 mg/kg). After fixing the rat in a stereotaxic frame, the animal was suspended by clamps on the spinal process on T_2 and on the tail to improve recording conditions. A craniotomy was performed, and the atlanto-occipital membrane was retracted to drain the cisterna magna. In addition, the cortical surface was exposed and the dura removed in order to locate the recording and stimulating electrodes.

A bipolar stainless steel stimulating electrode, insulated to within 0.2–0.5 mm of the tip and separated by a distance of 0.3 mm, was positioned in the SN and in some experiments also in the STH. Electrical stimulation consisted of rectangular current pulses of 0.05–0.20 ms, 50–150 μA delivered at 0.5–1 Hz. The cortical surface was covered with a mixture of warm liquid paraffin to prevent it from drying and to reduce brain pulsations. Intracellular recordings were made with a filament glass capillary tubing microelectrode (2.0 mm o.d) filled with a solution of 4% HRP (Sigma Type IV) in 0.05 M Tris buffer (pH 7.6) and 0.5 M KCl or K acetate. The electrode resistance measured in saline solution varied from 50–120 MΩ. A conventional technique was used for intracellular recording; oscillographic displays were photographed by a kimograph camera (Grass Instrument Co.), and experimental data were stored on magnetic tape (Vetter model B) for off-line data analysis. Neurons with resting membrane potential of 45 mV or more were intracellularly labeled with HRP by passing 2–5 nA depolarizing rectangular pulses of 150-ms duration at 3.3 Hz for 3–7 min.

One hour after injecting the neuron, an extra dose of urethane was administered (1.5 g/kg, i.p.), and the animal was perfused through the heart with saline solution followed by a mixture of 1% paraformaldehyde and 2% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4). The brain was removed, postfixed overnight in fresh fixative at 4°C, and cut into 50-μm serial transverse or sagittal sections by a vibratome. Sections were transferred into cold 0.05 M phosphate buffer and processed for HRP histochemistry with 0.05% 3.3'-diaminobenzidine tetrahydrochloride and 0.03% H_2O_2. The histological sections containing intracellularly labeled neurons were postfixed in 2% osmium-tetroxide in a phosphate buffer, mounted onto gel-coated slides, and air-dried before being dehydrated and cover-slipped. Other sections were mounted and stained with cresyl violet to determine the location of the stimulating electrodes or lesion sites. The recorded neurons and, in some cases, the morphological features of the intracellularly labeled PPN area neurons, were examined with a light microscope. Labeled neurons were serially reconstructed using a drawing tube and a X100 oil immersion objective. In three experiments, an ipsilateral coronal lesion just rostral to the STH was performed. The procedure, which has been explained in previous publications (Granata and Kitai 1989), was made to exclude the possibility of stimulating passing fibers originating from areas of the brain rostral to STH.

Results

Intracellular recording potentials were studied from 43 neurons located in the PPN area that generated action potentials more than 45 mV in amplitude and had resting membrane potentials larger than 48 mV. As mentioned earlier, the PPN area includes CTF, CNF, and PPNs. SN stimulation evoked IPSPs in 12 neurons, EPSPs in 9, and antidromic responses in 17. An inhibitory response, which was more probably the result of disfacilitation, was observed in 3 neurons, while SN stimulation did not evoke any response in 2 neurons. The majority of the recorded neurons fired spontaneously with an irregular pattern (frequencies of discharge varied between 10–100 Hz); however, those neurons responding with IPSPs to SN stimulation fired in general at higher frequencies. Recorded neurons were intracellularly labeled with HRP, and 3 of them were reconstructed from serial histological sections. The location of the recorded neurons is described in Fig. 1. The vast majority of the neurons were located in the caudal PPN area ventral and dorsal to the superior cerebellar peduncle, including the CNF. Only one of the labeled and reconstructed neurons is shown in Fig. 2. This neuron, which was located in the superior border of CNF, responded with IPSP to SN stimulation. The soma was fusiform (447 μm^2) and exhibited 6 primary dendrites. The axon originated from the soma and directed in a mediodorsalis direction. Many axon collaterals were observed. The dendritic field of this neuron extended 1594 μm dorsoventrally and 434 μm mediolaterally, spreading into the inferior colliculus. Another labeled neuron, also located in the caudal PPN in the superior border of CNF, responded with IPSP to SN stimulation. The soma was fusiform (230 μm^2) with 3 primary dendrites. The axon arose from the soma and directed dorsolaterally. The dendritic field of this neuron extended 81 μm dorsoventrally and 514 μm mediolaterally. One small labeled neuron was located ventral to the superior cerebellar peduncle in the caudal PPN. This neuron had a smooth soma which was oval in shape (8 × 11 μm). Three primary dendrites of different diameters (0.6–1.4 μm) arose from the soma. The dendritic field of this neuron sectioned sagitally extended 324 μm rostrocaudally and 255 μm dorsoventrally. We were not able to detect the axon of this cell.

Electrical stimulation of SN produced hyperpolarizing potentials in PPN area neurons (Fig. 3A). Hyperpolarization current applied through the recording electrode produced a decrease in the amplitude of the hyperpolarizing response (Fig. 3C, G). The reversal potential was obtained when the neuron was injected with − 1.4 nA, and the membrane potential reached −75 mV (Fig. 3G). These results indicated that the hyperpolarizing potentials were IPSPs. The onset latency of these IPSPs did not change in spite of changes in stimulus intensity (Fig. 3A); therefore, they were considered monosynaptic IPSPs. The latency of the IPSPs ranged from 1.0 to 8.5 ms (Fig. 3J). The distribution of these potentials (Fig. 3J), demonstrates a predominant group in which the onset latency varied from 1.0 to 2.0 ms (mean 1.4 ms); duration was 22.3 ms (±SD 14.5 ms), and the amplitude was 9.1 mV (±SD 4.9 mV). In the other four neurons, onset latency varied from 5.2 to 8.5 ms, with a duration of 28.2 ms (±SD 14.7 ms) and amplitude of 18.3 mV(±SD 15.6 mV) (Fig. 3J). On many occasions, the IPSPs evoked by SN stimulation were followed by rebound excitation, which produced several action potentials, sometimes with decreasing amplitude

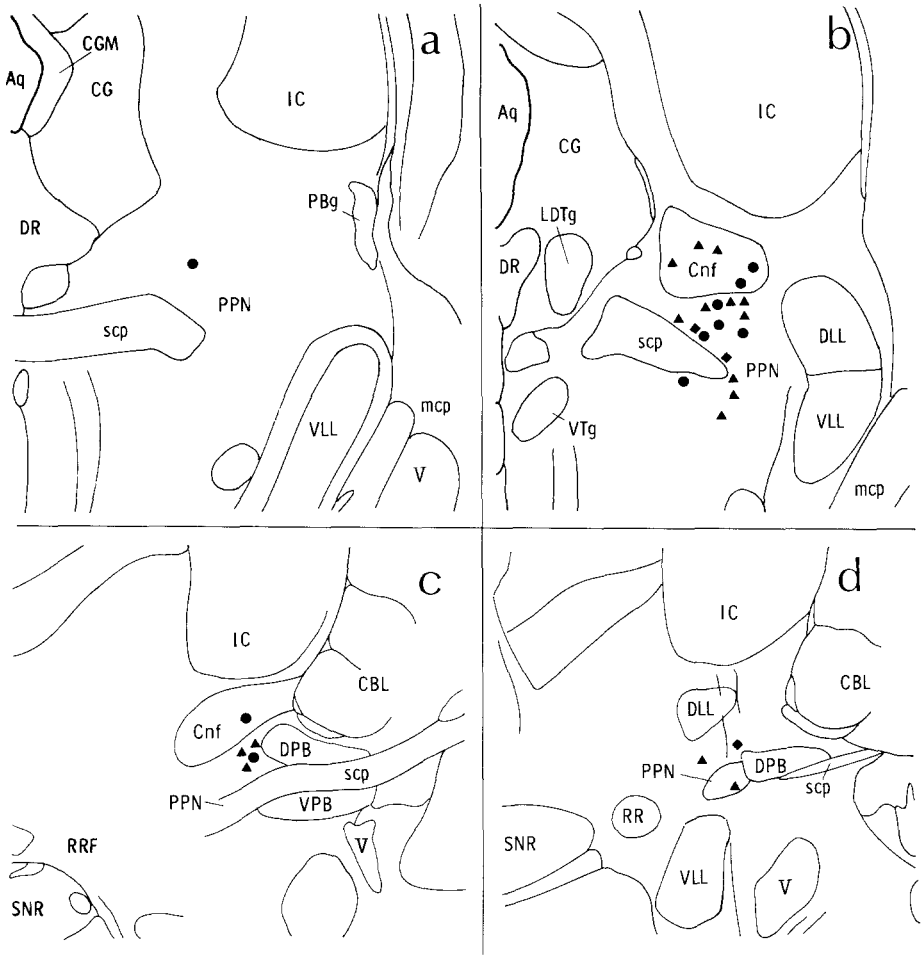

Fig. 1a–d. Location of intracellularly recorded neurons. **a, b** Schematic representation of coronal section of the brain stem at +1.2 mm and +0.7 mm from interaural line respectively. **c, d** Schematic representation of sagittal sections of the brain stem, 1.9 mm and 2.4 mm lateral from the middle line, according to Paxinos and Watson (1982). The closed circle indicates neurons receiving IPSP, the square indicates disfacilitation, and the triangles indicate antidromically activated neurons. *Abbreviations*: Aq = cerebral aqueduct; CG = central grey; CGM = central grey medial; CBL = cerebellum; Cnf = cuneiform nuclei; DLL = nucleus lateralis laminiscus (dorsalis); DPB = nucleus parabrachialis (dorsalis); DR = nucleus raphe dorsalis; IC = inferior colliculus; LDT_g = laterodorsal tegmental nuclei; mcp = middle cerebellar peduncle; PBg = nucleus parabigeminal; PPN = nucleus pedunculopontine; RR = nucleus retrorubral; RRF = retrorubral field; scp = superior cerebellar peduncle; SNR = substantia nigra reticulata; V = motor trigeminal nuclei; VLL = nucleus lateralis laminiscus (ventralis); VPB = nucleus parabrachialis ventralis; VTg = ventral tegmental nuclei

(Fig. 3B). This rebound excitation was observed in many neurons with resting membrane potential more negative than 50 mV; therefore, they are probably not the result of injury currents. This type of rebound excitation of PPN area neurons following IPSP could be misinterpreted as direct activation in extracellular in vivo studies (Scarnati et al. 1987).

In 9 neurons (6 experiments), EPSPs were evoked by SN stimulation. Of 9 EPSPs, 7 were characterized as monosynaptic (Fig. 4E). In this group of 7 monosynaptic EPSP, 3 neurons received only EPSP; in 4 neurons the EPSP was followed by an IPSP. The latency of these EPSPs was 2.4 ms (±SD, 1.1 ms). In 3 neurons, the electrical stimulation of STH also produced EPSP with a little longer latency. These results were observed in rats with chronic coronal lesion just rostral to the STH (Granata and Kitai 1989). These results indicate that the EPSPs evoked on PPN area neurons by SN stimulation could be the result of the activation of passing STH fibers. In 6 out of 9 neurons receiving EPSPs by SN stimulation, the EPSPs (4 of them monosynaptic) were followed by IPSPs (Fig. 3H, I). The neurons receiving EPSP-IPSP were in general spontaneously active and demonstrated a pacemaker-like pattern of discharge with slow depolarizing potential (SDP), which ended in a burst of action potentials (Fig. 3H, I). The shorter latency EPSPs produced by SN stimulation increased in magnitude and produced spike potentials when the membrane potential was at the more negative values (Fig. 3H, lower traces). On the other hand, the preceding EPSP was negligible when the membrane potential was at more positive values, but the IPSP increased in magnitude (Fig. 3H, upper traces). The magnitude of the membrane potential, in turn, depends on the SDP; for instance, when the stimulus is delivered at the beginning of the SDP, a bigger EPSP and spike potentials should be expected. Finally, the balance between the magnitude of the EPSP and the afterhyperpolarization ensuing the spike potentials on one hand and the magnitude of the IPSP on the other hand will ultimately determine the effectiveness of these inputs upon the pattern of discharge of PPN area neurons. In consequence, the responses of this type of PPN neurons to SN stimulation was modulated within the pacemaker-like cycle in that the effects varied with the phase when the stimulus was applied. The number of PPN neurons responding with IPSP to SN stimulation could have been underestimated in this study because the IPSP evoked by SN inputs was masked by the preceding EPSP in some neurons.

In 3 neurons, SN stimulation evoked inhibitory potentials (Fig. 4B), which decreased in magnitude when this neuron was depolarized and increased in magnitude dur-

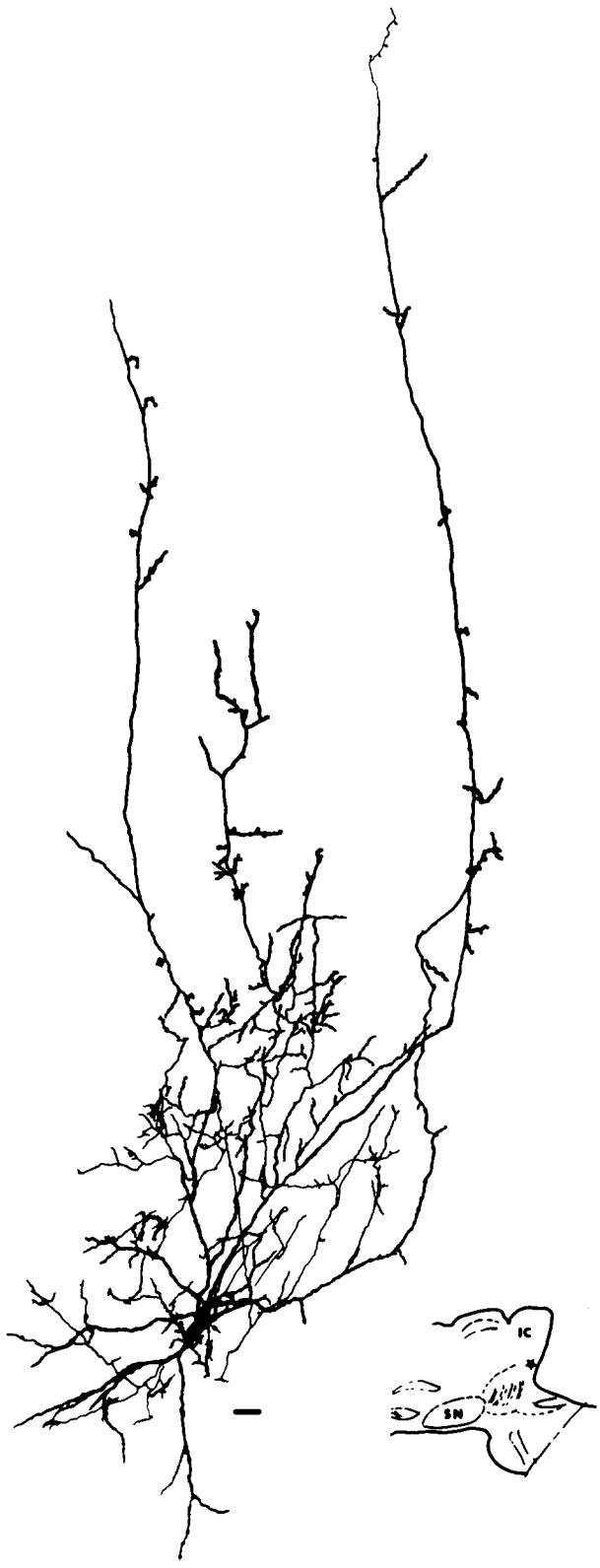

Fig. 2. Camera lucida reconstruction of one HRP-labeled neuron. The arrow indicates the axon of this neuron. The star in the inset shows the location of the reconstructed neuron in superior border of CNF. SN = substantia nigra; IC = inferior colliculus. The area encircled by dotted lines in inset represents the pedunculopontine area (PPN area). Bar = 40 μm

ing hyperpolarization (Fig. 4A, C). These inhibitory potentials could not follow high-frequency stimulation (Fig. 4D) (interstimulus interval of 2.5 ms); therefore, they were polysynaptically generated and are probably the result of disfacilitation. Antidromic responses were evoked on 17 neurons following SN stimulation (Fig. 5A–C; E, F). Antidromic spikes were all or none and demonstrated constant latency at threshold level of stimulation; no underlying potentials were noted when the action potential failed (Fig. 5A). These antidromic spikes could follow high frequency of stimulation (500 Hz) (Fig. 5B). Figure 5E and F show a long latency antidromically evoked response. In E, paired SN stimuli evoked constant onset latency repetitive responses. In Fig. 5F, the evoked response to the second stimulus was only observed due to collision of the first of the paired antidromic responses with a spontaneous action potential. The latencies of antidromic spikes varied from 0.56 ms to 8.60 ms. However, the frequency histogram (Fig. 5D) demonstrates two clearly separated peaks, one with a mean latency of 0.71 ms ($\pm$SD 0.18 ms) and a second with a mean latency of 5.16 ms ($\pm$SD 2.42 ms). In some neurons, it was possible to observe a rebound excitation after the afterhyperpolarization produced by the antidromically evoked action potential (Fig. 5C). Of these 14 antidromically stimulated neurons, 3 also responded with IPSPs. At higher intensity of stimulation (as shown in Fig. 3B), antidromic spikes were evoked first, followed by the IPSP with rebound excitation. At lower intensity of stimulation, only IPSPs were evoked. The latencies of antidromic responses were shorter than those of the IPSPs in these three observations.

Discussion

Our results demonstrate that electrical stimulation of SN in the rat evokes predominantly monosynaptic IPSP in PPN area neurons. These monosynaptic IPSPs were still observed after chronic hemicoronal lesion just rostral to STH. In addition, we have demonstrated that electrical stimulation of STH produced only monosynaptic EPSPs under these experimental conditions (Granata and Kitai 1989). Therefore the possibility that those IPSPs were produced by the stimulation of descending inhibitory projections was remote. In the cat, nigral projections also exert an inhibitory influence on PPN and CNF neurons (Noda and Oka 1986). Extracellular studies in vivo and intracellular studies in vitro in the rat demonstrated that electrical stimulation of SN induced either a decrease in the firing rate or IPSPs on PPN area neurons (Scarnati et al. 1987; Kang and Kitai 1990). In the present study, the reversal potential observed for the IPSP in PPN area neurons varied between -65 and -70 mV, a value close to the equilibrium potential for chloride in other CNS neurons (Coombs et al. 1955). Anatomical data have shown GABA-ergic neurons in the SN (reticulata) (Fonnum and Storm-Mathisen 1978). In addition, studies in vitro in the rat gave evidence that IPSPs elicited by SN stimulation on PPN neurons are blocked by the GABA

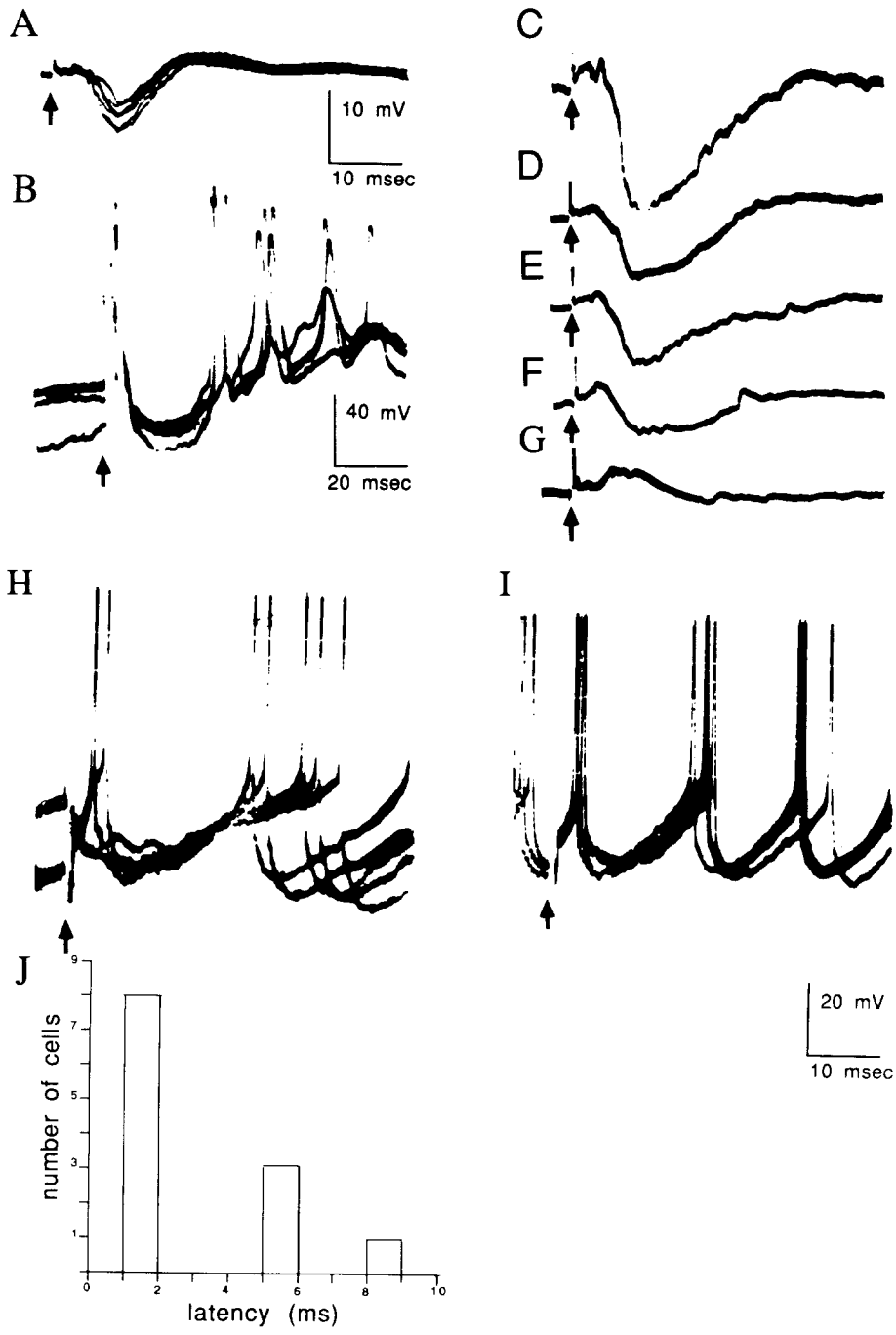

Fig. 3A–J. Inhibitory postsynaptic potentials evoked in the PPN area neurons following stimulation of SN (arrow). **A** IPSPs evoked with different stimulus intensities (arrow). The onset latency of IPSPs remained constant, indicating the monosynaptic nature of the response. **B** Antidromic and orthodromic responses (IPSPs) with rebound excitation. **C–G** Effect of hyperpolarizing and depolarizing currents on the IPSPs. (**D**: control; **C**: injection of +1.0 nA; **E–G**: injections of −0.2, −0.7, and −1.4 nA respectively.) **H, I** Excitatory postsynaptic potentials (EPSPs) followed by IPSPs. In **H**, depending on membrane potential at the stimulation time, the EPSPs generated action potentials (lower traces). Voltage and time calibration in I also applies to C–H. **J** Frequency histogram of IPSP latencies of PPN area neurons following SN stimulation

antagonist bicuculine (Kang and Kitai 1990). The present results, taken together with these previous observations, would suggest that the IPSPs mediated by nigro-PPN projections use GABA as a neurotransmitter.

Using the anterograde tracer lectin Phaseolus vulgaris, it has been demonstrated that nigral afferents from SN reticulata impinge on dendrites of PPN projection neurons (Spann and Grofova 1988). Moreover, more recent publications demonstrate that axon terminals of projection fibers, originating from SN reticulata, make symmetric synaptic contacts with both somata and dendrites in PPN neurons (Nakamura et al. 1989). These reports give anatomical background to our physiological data. Other projections from SN reticulata, such as to the superior colliculus and thalamus, have inhibitory effects and use GABA as neurotransmitter (Chevalier et al. 1981; Di Chiara et al. 1979).

In some neurons a rebound excitation with depolarizing potentials following the IPSP elicited by SN stimulation was observed. Kang and Kitai (1990) also observed this rebound depolarization in in vitro preparation, and they reported that it is related to the level of membrane potential. In accordance with this report as well as previous reports from this laboratory, the time course of these

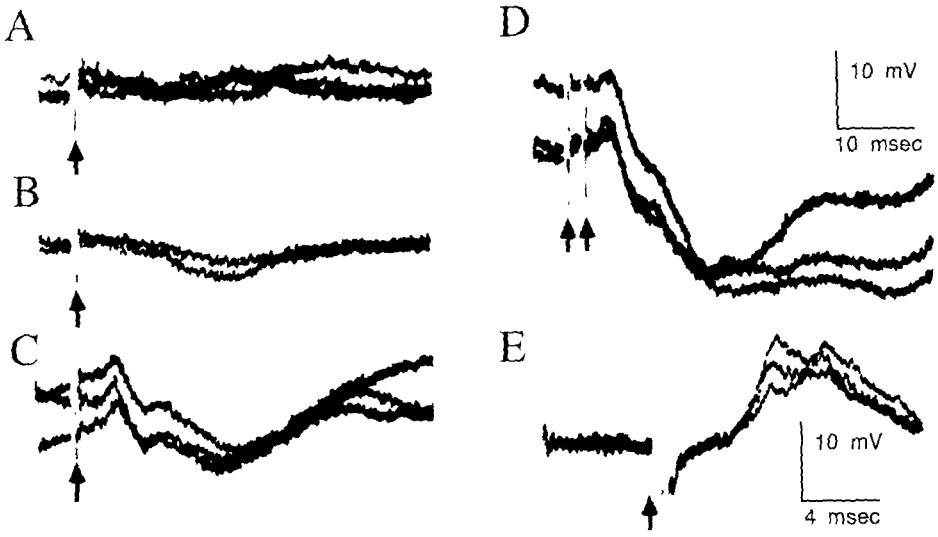

Fig. 4. A–C Effect of depolarizing (+0.5 A) (A) and hyperpolarizing (−0.75 nA) (C) on inhibitory potentials (B, control) evoked by SN stimulation on a PPN area neuron. **D** (Same neuron) These inhibitory potentials could not follow repetitive stimulation. **E** Monosynaptic EPSPs evoked in a PPN area neuron by SN stimulation

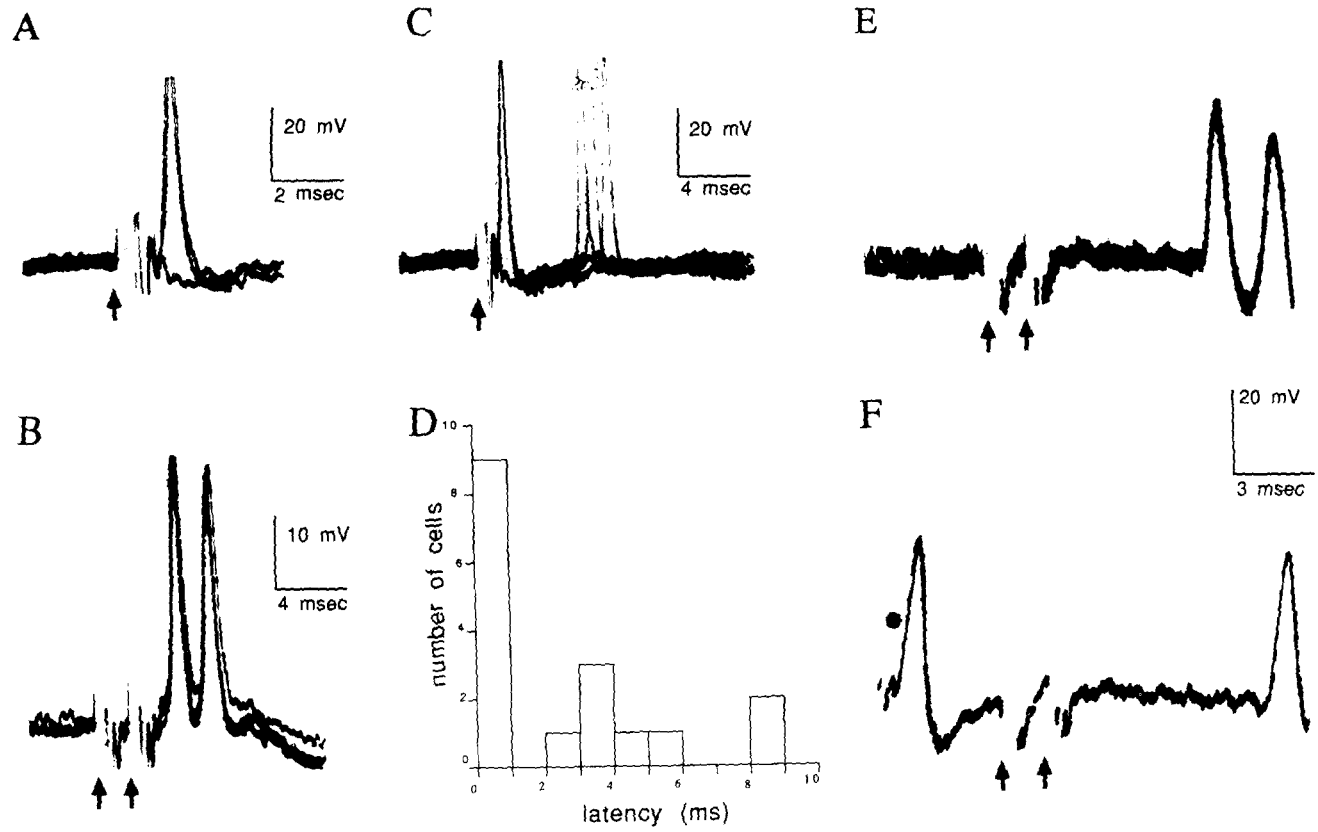

Fig. 5A–F. Antidromic responses of a PPN area neuron following SN stimulation. **A, C** Antidromic responses to threshold level of stimulation. **B** Antidromic responses follow high frequency of stimulation (500 Hz). **D** Frequency histogram of antidromic spike latencies. **E, F** Long latency antidromic responses of a PPN area neuron to paired SN stimuli. In **F**, a spontaneous spike collided with the first antidromic action potential

depolarizing potentials is incompatible with sodium current. The rebound excitation is probably not synaptically mediated but could be the result of voltage-dependent conductances activated by such hyperpolarizing mechanisms as IPSP or the afterhyperpolarization ensuing antidromic spikes. Our data in vivo indicate a reciprocal electrophysiological influence exerted by SN and PPN area neurons on each other; stimulation of SN produces synaptic, as well as antidromic, responses in PPN neurons. Several neuroanatomical studies support these results (Beckstead et al. 1979; Beckstead 1983; Carpenter et al. 1981a, b; Hammond et al. 1983; Jackson and Crossman

1981; Moon-Edley and Graybiel 1983; Nomura et al. 1980; Sugimoto and Hattori 1984; Saper and Loewy 1982; Spann and Grofova 1989; Scarnati et al. 1987; Beninato and Spencer 1987; Clarke et al. 1987; Gould et al. 1989). The latency time of IPSPs reported in this study is very similar to those found in vitro by Kang and Kitai (1990), suggesting that similar types of neurons have been analyzed in both studies. The latency time of antidromic responses in our experiments clearly demonstrates two different groups of neurons. These two groups were also predominantly present in the frequency histogram of antidromic latencies observed in extracellular studies (Scarnati et al. 1987). In addition, the latencies of these antidromic responses are compatible with PPN projection neurons to SN (Scarnati et al. 1984, 1986).

Electrical stimulation of SN evoked monosynaptic EPSP or EPSP followed by IPSP in some PPN neurons. The results are consistent in some cases with the activation of descending excitatory fibers originated in the STH. An alternative explanation for these EPSP could be the result of stimulation of recurrent collaterals to the PPN area originating from ascending projections terminating or passing through the SN. This possibility is supported by (1) our previous anatomic data showing that projection PPN area neurons had axon collaterals (Granata and Kitai 1989) and (2) the action of rostrally projection PPN neurons, which is mainly excitatory (Scarnati et al. 1984, 1986).

The majority of these neurons, which were analyzed electrophysiologically, were located in the caudal PPN area, mostly dorsal to the superior cerebellar peduncle, involving the CNF. Some neurons were also located lateral or ventral to the superior cerebellar peduncle. We did not observe any difference in terms of their regional distribution between PPN projection neurons and those PPN neurons receiving orthodromic inputs.

Our results show a reciprocal connection between the SN reticulata and PPN area neurons. The nature of SN reticulata inputs to PPN is found to be monosynaptic and inhibitory, while previous studies indicate that the action of PPN cholinergic neurons were reported to be excitatory to their target neurons (Clarke et al. 1987; Deschenes and Hu 1990; Hu et al. 1989; Scarnati et al. 1986). Even though the STH nucleus was demonstrated to be a major excitatory input to the SN reticulata (Kitai and Kita 1987; Nakanishi et al. 1987), PPN is an additional source of excitatory inputs to SN reticulata, and the excitation of SN reticulata results in feedback inhibitory regulation of PPN neurons.

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