Ascending Inhibition of Nociceptive Neurons in the Thalamic Intralaminar Nuclei Following Conditioning Stimulation of the Mesencephalic Periaqueductal Gray

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Abstract

The nucleus raphe dorsalis (NRD) or the ventromedial part of the mesencephalic periaqueductal gray matter (PAG) which is immediately adjacent to the PAG were stimulated in urethane chloralose-anesthetized cats. Single unit activities were recorded from the neurons in the nucleus centralis lateralis (CL) and nucleus parafascicularis (Pf) of the thalamic intralaminar nuclear group. Of 63 CL and 37 Pf units recorded, 13 and 5 units, respectively, were excited by the NRD/PAG stimulation. In the remaining 50 CL and 32 Pf units, effects of NRD/PAG stimulation on responses evoked by electrical stimulation of the splanchnic nerve (SPL), dorsal ramus of the C₂ nerve (C₂), tooth pulp afferents and/or mesencephalic reticular formation (MRF) were studied. In 12 CL and 9 Pf units, the NRD/PAG conditioning stimulation inhibited responses to peripheral and/or MRF inputs. In 38 CL and 23 Pf units, the NRD/Pf stimulation had neither excitatory nor inhibitory effect. These results were in contrast with our previous findings that stimulation of the NRD or its adjacent ventromedial PAG invariably inhibited responses of nociceptive neurons in the shell region of the VPL to visceral afferent input.

Key Words : thalamus, intralaminar nuclei, nociception, antinociception, ascending inhibition

INTRODUCTION

Pain is an unpleasant sensory-emotional experience dependent on the individual and the situation in which it occurs. Nociceptive stimuli unnoticed under some circumstances may be unbearable under others. Beecher⁶⁾ compared the analgesic requirements of soldiers wounded in battle during World War II with civilians undergoing elective surgery after the war. Despite the greater severity of the soldiers' wounds, their analgesic needs were much less than those of the civilians. The stressful situation associated with combat obviously influenced the pain, implying the existence of central nervous mechanisms capable of modulating pain perception.

Reynolds²⁵⁾ first described the phenomenon of stimulation produced antinociception (SPA) by electrical stimulation in the central gray matter of the rat. Subsequent studies showed that the periaqueductal and periventricular areas in the rat are effective in suppressing nociceptive flexion reflexes and/or aversive behaviors^{18,19)}. Stimulation in the area of the nucleus raphe dorsalis (NRD) in the cat was also successful in producing antinociception¹⁷⁾.

Soon after SPA was discovered, the neural pathway that mediates this phenomenon was defined. Two findings pointed to the existence of a descending antinociceptive pathway that terminates on nociceptive neurons in the spinal cord. First, electrical stimulation of periaqueductal gray matter (PAG) was found to inhibit responses of spinal cord neurons to noxious stimuli^{11,17)}. Second, discrete lesion of the dorsolateral funiculus in the spinal cord abolished the suppression of nociceptive flexion reflexes and/or aversive behaviors due to PAG stimulation⁵⁾.

Further investigation of SPA provided considerable detail about the neural circuitry involved; PAG neurons make excitatory con-

nections in the ventromedial medulla oblongata. Neurons in this region in turn make inhibitory connections in laminae I, II and V of the spinal cord. The ultimate inhibition of the transmission of nociceptive information thus occurs at the initial stage in the dorsal horn of the spinal cord by selective inhibition of nociceptive neurons⁷⁾.

Evidence was later found to indicate that nociception can also be modulated at a supraspinal level. In rats in which the descending pathway was selectively disrupted, the PAG stimulation-produced suppression of spinally mediated tail flick reflex was significantly reduced. In contrast, PAG stimulation-produced suppression of supraspinally mediated hot plate response was unaffected by the same brainstem lesion²⁰⁾. Electrical stimulation in the nucleus raphe medianus¹³⁾ or in the NRD of the cat^{2,24)} inhibits nociceptive responses of neurons recorded in the nucleus parafascicularis (Pf) of the medial thalamus. The inhibition involves a postsynaptic inhibitory mechanism in Pf neurons¹⁾.

Recently we have found in the cat that stimulation of the NRD and its adjacent ventromedial PAG inhibits responses of nociceptive neurons in the shell region of the nucleus ventralis posterolateralis (VPL) of the lateral thalamus to visceral afferent inputs, and obtained evidence to indicate the existence of pain modulating systems by way of ascending pathways in addition to the well established descending paths^{12,21)}.

In the present study, we have studied effects of stimulating the NRD or its adjacent ventromedial PAG on responses of nociceptive neurons in the intralaminar nuclei to peripheral and supraspinal afferent inputs.

METHODS AND MATERIALS

Experiments were carried out on adult cats. Each animal was initially anesthetized with ketamine hydrochloride (20 mg/kg), and anes-

thetia was maintained with an intravenous dose (3.5 ml/kg) of urethane/chloralose solution (urethane 125 mg/ml and chloralose 10 mg/ml) supplemented as required. A thermistor probe was placed in the esophagus and the body temperature was maintained at $37 \pm 0.5^\circ\text{C}$ by an electric heating pad under the abdomen, and by an infrared lamp. A pair of bipolar stimulating electrodes was placed around the greater splanchnic nerve (SPL). Another pair of bipolar stimulating electrodes was applied to the greater occipital nerve (ramus dorsalis of the 2nd cervical nerve; C_2) which innervates the pinna and dorsal neck muscles. The stimulating electrodes were sealed in place with a low melting point paraffin wax.

The maxillary and mandibular canine teeth on both sides were prepared for electrical stimulation. In each canine tooth, small cavities, 1 mm in diameter, were drilled into the predentine at two sites approximately 3 mm apart on the labial side. The cavities were deepened until tooth pulp blood vessels were visible. A silver wire, 0.4 mm diameter, was placed in each cavity and then the cavity was filled with firmly packed dental amalgam. Finally dental resin was placed over the amalgam fillings, and the silver wires were threaded through polyethylene tubing.

After preliminary surgery, the prepared animal was placed in the prone position on a shock-proof table. The head was rigidly fixed in a stereotaxic instrument.

Craniotomies were carried out over the thalamus (to allow access for microelectrode exploration) and the midbrain in order to allow bipolar, concentric stimulating electrodes to be placed.

During exploration with microelectrodes, neuromuscular transmission was blocked by intravenous administration of pancuronium bromide (0.4 mg/kg). Subsequently, the animal was artificially respired through an endotracheal

tube. End-tidal CO_2 % was monitored and maintained at 3.5–4.5 %. The mean arterial pressure was continuously monitored by a catheter in the right femoral artery and was kept above 90 mmHg if necessary by infusion of lactate-Ringer solution. The level of anesthesia was checked intermittently by allowing the animal to recover from the relaxing drug. A bilateral pneumothorax was made by cutting through the parietal pleura and the thoracic vertebral column was elevated to ensure the integrity of the pneumothorax.

The medial thalamus was explored with glass capillary microelectrode penetrations. Glass capillary microelectrodes were filled with 2 % Pontamine sky blue in 0.5 M Na acetate.

The peripheral receptive field properties of single units in the medial thalamus were assessed using a variety of mechanical stimuli: gentle brushing of the skin with a soft brush, pressure applied to a fold of skin using a pair of broad-tipped forceps, and pinching with a pair of fine rat-toothed forceps. Single unit activities were displayed on an oscilloscope and led to a window discriminator. Discriminator pulses were used by a spike counter for construction of peristimulus time histograms. The firing rates and window discriminator pulses were recorded on a chart recorder. Units were also tested for tooth pulp, SPL and C_2 inputs. All nociceptive units with one or more of these inputs were tested for effects of electrical stimulation in the NRD or its adjacent ventromedial PAG. Unit responses and stimulus artefacts were displayed by a dot raster method using window discriminator pulses.

The locations of units of interest were marked by extruding a small amount of Pontamine sky blue from the electrode electrophoretically ($5 \mu\text{A}$ DC current (electrode negative), passed for 10 min).

At the conclusion of each experiment, the

Fig. 1 A CL unit.

A: receptive field. **B**: location of the unit in CL indicated by an arrow. **C**: site of stimulation in MRF indicated by an arrow. **D**: dot raster display of responses to electrical stimulation of contralateral upper canine tooth pulp (CUC), contralateral lower canine tooth pulp (CLC), ipsilateral lower canine tooth pulp (ILC), ramus dorsalis of the second cervical nerve (C_2), SPL and MRF. Stimulus artefacts are indicated by arrows.

stimulation sites in the midbrain were lesioned electrolytically, by passing a current of 2 mA DC between the poles of the stimulating electrode for 2 min. Animals were then deeply anesthetized, and perfused through the beating heart with 1 l of a solution of 0.5 % potassium ferrocyanide in normal saline, followed by 2 l of 10 % formol saline. Serial sections (50 μ m thick) were cut, stained with Cresyl violet, and the locations of both the stimulation and recording sites were checked.

RESULTS

Recordings were made from 100 nociceptive units in the intralaminar nuclei. They were located either in the nucleus centralis lateralis (CL) or in the nucleus parafascicularis (Pf).

Nucleus centralis lateralis units

Sixty three units were recorded from the CL. Of these, 62 units had a receptive field in the bilateral (57 units), or contralateral (5 units) trunk. These units usually responded to heavy pressure applied to the deep tissues rather than

Fig. 2 Responses of a CL unit to PAG stimulation.

A: site of stimulation indicated by an arrow. **B**: dot raster display of responses to PAG stimulation. Stimulus artefacts are indicated by an arrow. Repetition rate of PAG stimulation was 0.5 Hz.

the skin. The receptive field extended into the forelimb (31 units) and/or hindlimb (34 units). The four limb receptive field was confined to the proximal part of the forelimb (13 units) and/or hindlimb (16 units). Twenty eight units were excited by stroking across the bilateral (24 units) or contralateral (4 units) corneal surface with a blunt end of a glass rod. Noxious pinch applied to the bilateral (17 units) or contralateral (9 units) pinna excited 26 units, and that applied to the bilateral (4 units) or contralateral (1 units) tongue excited 5 units. Eight units responded to

Fig. 3 Inhibition of responses of a CL unit to SPL stimulation following conditioning stimulation of ventromedial PAG.

A: dot raster display of responses to SPL stimulation. Arrows indicate stimulus artefacts. Repetition rate of SPL stimulation was 0.5 Hz.

Fig. 4 Mean time course of inhibition of responses of 10 CL units to peripheral afferent inputs. Mean and standard error are shown at different conditioning-test intervals.

firm pressure applied to the bilateral (5 units) or contralateral (3 units) face. Nineteen units were excited by tapping the dorsum of bilateral (14 units) or contralateral (5 units) nose. Electrical stimulation of tooth pulp excited 11 units. All 4 canine tooth pulps were effective in 6 units. **Figure 1** illustrates the receptive field, location in the thalamus, stimulation site in the midbrain

Fig. 5 Inhibition of responses of a CL unit to MRF stimulation following conditioning stimulation of ventromedial PAG.

A: dot raster display of responses to MRF stimulation. Stimulus artefacts are indicated by arrows. **B:** time course of inhibition following PAG conditioning stimulation.

tegmentum and responses to both peripheral and mesencephalic reticular formation (MRF) inputs of a CL units.

Effects of electrical stimulation of the NRD/PAG were examined in all the CL units recorded. Single shock stimulation with a 0.1 ms square pulse at an intensity less than 500 μ A excited 13 CL units (20.6%). An example is illustrated in **Fig. 2**. The receptive field, location in the thalamus and responses to afferent inputs of this unit were already shown in Fig. 1. Following single shock stimulation of the ventromedial PAG at 350 μ A, the unit responded with 1 to 6 spikes. The latency of the responses ranged from 3.6 to 10 ms.

Excluding the units which were excited by the NRD/PAG stimulation, or were unresponsive to SPL, C_2 or tooth pulp inputs, effects of NRD/PAG conditioning stimulation on the responses to peripheral afferent inputs were studied. The conditioning stimulation consisted of a train of 5 pulses at 400 Hz. The duration of individual pulse was 0.1 ms, and the stimulus intensity was less than 1 mA. A total of 40 units were subjected to the study, and inhibition was observed in 10 units (25.0%). Inhibition

Fig. 6 Mean time course of inhibition of responses of 6 CL units to MRF stimulation following conditioning stimulation of NRD/PAG.

produced by conditioning stimulation of the ventromedial PAG immediately adjacent to the NRD is illustrated in **Fig. 3**. In this experiment, the test stimulation was delivered to the contralateral SPL. The intensity of conditioning stimulation was 500 μ A. The maximum inhibition was 80%, and was observed at 30 ms conditioning-test interval. The maximum inhibitory effect was maintained for about 50 ms, and the response gradually returned to the control level. The mean time course of NRD/PAG stimulation-produced inhibition of responses to peripheral afferent inputs observed in 10 CL units is shown in **Fig. 4**. The maximum inhibition was obtained

Fig. 7 A Pf unit excited by PAG stimulation.

A: receptive field. **B**: location of the unit. **C**: site of stimulation in the PAG. **D**: dot raster display of responses of the unit to PAG stimulation.

at 30 ms conditioning-test interval, and the inhibition outlasted 100 ms.

Forty CL units were transsynaptically excited by electrical stimulation of the MRF. Of these, 12 units were excited by electrical stimulation of the NRD/PAG. In the remaining 28 CL units, effects of NRD/PAG conditioning stimulation on the responses evoked by the MRF stimulation were studied. Inhibition was observed in 6 units (21.4%). An example of PAG stimulation-produced inhibition of responses to the MRF stimulation is illustrated in **Fig. 5**. The responses to the MRF stimulation were completely inhibited at 30~60 ms conditioning-test interval. The mean time course of NRD/PAG stimulation-produced inhibition of responses to the MRF stimulation is shown in **Fig. 6**. The maximum

inhibition was observed at 30 ms conditioning-test interval, and the inhibition outlasted 100 ms.

Twenty seven CL units responded to both peripheral and MRF inputs. Of these, 6 units were excited, and 4 units were inhibited by the NRD/PAG stimulation. In the latter 4 units, responses to both peripheral and MRF inputs were inhibited in parallel.

In the total population of 63 CL units subjected to the study of effects of NRD/PAG stimulation, inhibition of responses to peripheral and/or MRF input was observed in 12 units (19.0%). In 38 units (63.0%), the NRD/PAG stimulation had neither excitatory nor inhibitory effect.

Nucleus parafascicularis units

Thirty seven nociceptive units were recorded from the nucleus parafascicularis (Pf). Of these,

Fig. 8 Inhibition of responses of a Pf unit to SPL stimulation following conditioning stimulation of the ventromedial PAG. **A**: dot raster display of responses to SPL stimulation. **B**: time course of inhibition following PAG conditioning stimulation.

30 units had a receptive field in the bilateral (23 units) or contralateral (7 units) trunk. The receptive field in the trunk extended into the forelimb (27 units) and/or into the hindlimb (18 units). The forelimb and hindlimb receptive fields were confined to the proximal part in 8 and 4 units, respectively. Twenty three units were responsive to noxious pinch applied to the bilateral (15 units) or contralateral (8 units) pinna. Mechanical stimulation of the cornea was effective in 12 units. The corneal receptive field was bilateral in 10 units and contralateral in 2 units. Five units had a nociceptive field in the bilateral (2 units) or contralateral (3 units) tongue. Electrical stimulation of bilateral (9 units) or contralateral (2 units) tooth pulp excited 11 units.

Electrical stimulation of the NRD/PAG excited 5 Pf units (13.5%) at an intensity less than 500 μ A. An example is illustrated in **Fig. 7**. In this experiment, the PAG was stimulated at

Fig. 9 Mean time course of inhibition of responses of 9 Pf units to peripheral afferent inputs following conditioning stimulation of NRD/PAG.

450 μ A. The response consisted of a single or double spike. The latency was 5.0~10.8 ms. In the remaining 32 units, effects of NRD/PAG conditioning stimulation at an intensity less than 1 mA on responses evoked by electrical stimulation of SPL, C₂ and/or tooth pulp were studied. Inhibition was observed in 9 units (28.1%). **Figure 8** illustrates a Pf unit in which the PAG conditioning stimulation at 500 μ A inhibited responses to SPL stimulation. The maximum inhibition was observed at 30 ms conditioning-test interval. The degree of inhibition at this interval was 82%. The inhibition outlasted 120 ms. The mean time course of NRD/PAG stimulation-produced inhibition of responses to peripheral afferent inputs in 9 Pf units is shown in **Fig. 9**. The time course was much the same as that in CL units.

Fifteen Pf units were excited by the MRF stimulation. The responses to the MRF stimulation was inhibited following conditioning stimulation of the NRD/PAG in 2 units. In these 2 units, responses to both SPL and C₂ stimulation were also inhibited by the conditioning stimulation.

In the total population of 37 Pf units studied, 5 units (13.5%) were excited, and 9 units (24.3%) were inhibited following the NRD/PAG stimulation. The remaining 23 units (62.2

Excitation

Inhibition

No Effect

Fig. 10 Sites of stimulation in NRD and its adjacent PAG.

Sites in which stimulation evoked excitation, inhibition or no effect are shown. Filled circles indicate sites stimulated in the experiments studying CL units. Open circles indicate sites stimulated in the studies of Pf units.

%) were unaffected by the stimulation.

Sites of conditioning stimulation

Figure 10 summarizes the sites of conditioning stimulation in the present study. The stimulating electrode was placed in the NRD or its adjacent ventromedial PAG, irrespective of the effects produced by the stimulation. In 8 animals, stimulation of the same site had an excitatory or inhibitory effect on one CL unit, but had no effects on another CL unit. In one cat, both excitatory and inhibitory effects were observed by the stimulation of the same site. Similarly, in 9 animals, stimulation of the same site produced excitatory or inhibitory effect on one Pf unit, but had no effect on another Pf unit.

These results suggest that stimulation of the NRD and its adjacent PAG has excitatory or inhibitory effect on some CL and Pf units, but the stimulation has no effect on about 60 % of the total population of both CL and Pf units.

DISCUSSION

Nociceptive fibers enter the spinal cord through the dorsal root, and synapse in the

dorsal horn, notably in laminae I, II and V. Nociceptive impulses then ascend the neospinothalamic tract in the ventrolateral funiculus to the shell region of the VPL. This lateral system finally projects to the somatosensory cortex, where it provides information regarding the sensory-discriminative aspect of pain²⁷.

There are also nociceptive relay neurons in laminae VII and VIII of the spinal cord. Projection fibers from these laminae ascend as the paleospinothalamic tract to the medial thalamus and terminate in the anterior group of the intralaminar nuclei, i. e., nuclei centralis lateralis, paracentralis and centralis medialis^{3,14}. There are also polysynaptic pathways from the spinal cord to the medial thalamus via brain stem structures, in particular, the reticular formation. Not only the anterior intralaminar group, but also the nucleus parafascicularis (Pf) of the posterior intralaminar group receive peripheral afferent input through the polysynaptic ascending pathways¹⁶. The intralaminar nuclear group has diffuse efferent connections with cortical and subcortical structures including the limbic

system¹⁵⁾, and thus subserves the emotional-motivational aspect of pain²³⁾. Recently, we have found that conditioning stimulation in the NRD or its adjacent PAG invariably inhibits responses of nociceptive neurons in the shell region of the VPL to test stimuli applied to visceral sympathetic nerves^{12,21)}. In the present study, we stimulated the same region of the midbrain, i. e., the NRD or its adjacent PAG. The stimulation was found to produce inhibition of responses of some nociceptive neurons in both the CL and Pf to peripheral afferent inputs. Responses of CL and Pf neurons to electrical stimulation of the MRF were also inhibited. These findings suggest the existence of a supraspinal inhibitory mechanism acting upon the medial system. However, a great majority of nociceptive neurons in both the CL and Pf was not inhibited by the conditioning stimulation in the NRD or its adjacent PAG. Since conditioning stimulation of the same region invariably inhibited the responses of nociceptive neurons in the VPL to visceral afferent input, the antinociceptive system originating from the NRD and its adjacent ventromedial PAG appears to be primarily for the lateral system of the ascending pain pathways which projects to the somatosensory cortex via the shell region of the VPL.

In the present study, it was also found that some nociceptive neurons in both the CL and Pf were excited by electrical stimulation of the NRD or its adjacent PAG. There is considerable evidence of efferent connections of the NRD with the thalamic intralaminar nuclei. HRP injected into the Pf retrogradely labels neurons within the NRD in the cat⁹⁾. Conversely, anterograde labeling can be observed in the Pf following microinjection of HRP conjugated with wheat germ agglutinin into the NRD in the rat²²⁾. Dorsal raphe injection of radioactive amino acids results in labeled terminals in the intralaminar nuclear group in the cat and rat^{4,8,26)}. Electrical stimula-

tion in the CL of the rat evokes antidromic excitation of NRD neurons¹⁰⁾.

It is generally considered that the efferent connections of the NRD with the intralaminar nuclei reflect inhibitory role played by the NRD. The present study revealed that this is not necessarily the case. In clinical practice, nervousness and anxiety are produced by ventral PAG stimulation²⁸⁾. The excitation of nociceptive neurons in both the CL and Pf as revealed in the present study may be an explanation for these undesirable side effects.

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