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Identification of Central Trigeminal Nociceptors and the Effects of Nitrous Oxide

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Physiologic and pharmacologic properties of the nucleus caudalis of the trigeminal complex were studied using an extracellular microelectrode recording technique in unanesthetized, mechanically ventilated, decerebrate cats after removal of the neural arch of the first cervical spine. Central trigeminal nociceptors were identified in the magnocellularis portion of the dorsal horn of the first cervical segment of the spinal cord. This finding resolved an apparent "paradox" reported previously. Cells responding to low-threshold cutaneous stimuli applied to the ipsilateral face were found dorsal and rostral to the central trigeminal nociceptors. Nitrous oxide (75 per cent) suppressed the spontaneous firing frequency of the central trigeminal nociceptors by 31–35 per cent, but facilitated spontaneous activity of the low-threshold cutaneous receptors of the nucleus caudalis by 20–31 per cent. The differential effects of nitrous oxide on trigeminal neurons were analogous to the effects of nitrous oxide on the nuclear aggregates of the dorsal horn of the feline lumbar spinal cord. (Key words: Central trigeminal nociceptors; Nucleus caudalis; Nitrous oxide.)

IN CONTRAST TO the fact that cells responsive to nociceptive stimuli have been localized in Rexed's[1] laminae 1 and 5,[2-4] trigeminal neurons responding to painful stimuli only have defied identification for a number of years.[5-9] Indirect evidence suggesting that the nucleus caudalis of the trigeminal complex may be associated with facial nociception[9-20] has led to much study of this area in search of cells responsive to noxious stimuli.

Although a recent report[21] indicates the probable presence of such units in the marginal zone of the trigeminal nucleus caudalis, no histologic identification has been presented.

In the present investigation, we re-explored the physiologic properties of the nucleus caudalis in search of cells uniquely responsive to nociceptive stimuli, identified histologically a central representation for trigeminal nociception, and studied the pharmacologic effects of nitrous oxide upon the spontaneous activity of neurons within the caudalis nucleus.

Methods

Fourteen cats, each weighing 2.5–5 kg, were anesthetized with halothane, nitrous oxide, and oxygen for tracheostomy and cannulation of the femoral artery and vein. Anesthesia was maintained with controlled respiration using a volume-cycled ventilator with the aid of intravenous infusion of gallamine triethiodide (5–7 mg/kg/hour). By adjusting the degree of mechanical ventilation, end-expiratory P_{CO_2} was maintained at 34 ± 2 torr, as determined by infrared analyzer. Femoral arterial pressure was continuously monitored and data obtained from animals with arterial pressures below 80 torr systolic at any time were excluded from the study. Rectal temperatures were kept at 37 ± 1 C using a water mattress with a thermal servo-control mechanism. Decerebration was accomplished by bilateral electrolytic lesions in the mesencephalic reticular formation, using dc 20 mA for 10 seconds. Following decerebration the animals were ventilated with 100 per cent oxygen, halothane and nitrous oxide being eliminated, using a nonrebreathing circuit. The animal's head was fixed in a Horsley-Clarke stereotaxic apparatus that allowed 45 degrees of cervical flexion. The animal was then suspended by means of bilateral hip bars to increase venous

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FIG. 1. Unit activity of a central trigeminal nociceptor. Activity is evoked uniquely by a high-threshold cutaneous stimulus applied to the ipsilateral face. Stimulation by a needle evokes single-unit activity, while bending of hairs does not.

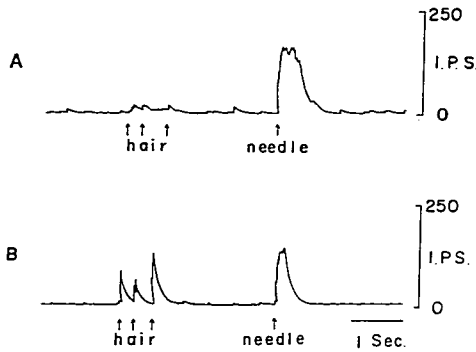

FIG. 2. Polygraph display of firing frequency of a central trigeminal nociceptor (*A*) and that of a low-threshold cutaneous central mechanoreceptor (*B*); the latter responds to low-threshold cutaneous stimulation, such as bending a hair, as well as to the high-threshold stimulus. The former, however, responds to the noxious stimulus only.

return and to avoid abdominal pressure during mechanical ventilation, in order to minimize brain movement. Using a midline incision, upper cervical laminectomy was performed, removing the posterior arch of the first cervical vertebra, and opening the dura over the obex to the second cervical arch. Activity of cells in the nucleus caudalis was then sampled from the level of the obex down to the second cervical arch, using Transidyne microelectrodes (1–2-μm exposed tips) which were advanced with a hydraulic micromanipulator. A mixture of bone wax and mineral oil warmed to body temperature covered the microelectrode insertion site to minimize respiratory movement of the spinal cord and to maintain local temperature. Signals were recorded through a differential FET ac preamplifier and a Tektronix oscilloscope, and were also stored on magnetic tape and processed by computer using a DEC PDP12 general-purpose digital computer.

Low-threshold stimuli included bending hairs and directing puffs of air to the receptive field, and high-threshold stimuli included squeezing, pinching, needle-pricking, and application of an alligator clamp.

A period of no less than four hours was allowed to elapse between anesthesia and decerebration and control recording.

Following localization of individual cells in the nucleus caudalis, the spontaneous firing rate was continuously counted electronically and recorded on a polygraph: 1) for 20–30 minutes during the control period with 100 per cent oxygen; 2) during administration of 75 per cent nitrous oxide until a new steady state was achieved (10–20 minutes); 3) during recovery from nitrous oxide anesthesia (nonrebreathing oxygen) until the control level of firing rate was obtained following the cessation of nitrous oxide administration (10–20 minutes). Only units from which a complete

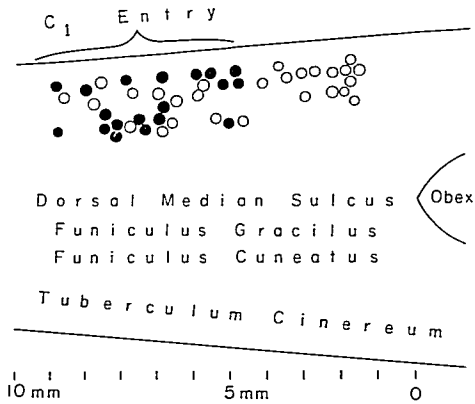

FIG. 3. Diagrammatic representation of areas in which central trigeminal nociceptors (solid circles) and low-threshold central mechanoreceptors (open circles) were located. Beneath the neural arch of the first cervical spine, occasionally, relatively well-developed filamentous fibers of the first cervical dorsal root were found. Central trigeminal nociceptors were found only in the caudal portion of the nucleus caudalis along the tuberculum cinereum beneath the first cervical neural arch. Low-threshold mechanoreceptors were located dorsally and, for the most part, rostral to the nociceptors.

control–gas–recovery cycle could be obtained were included in the analysis of data.

In three animals there were relatively well-developed filaments of the first cervical dorsal root. These were cut in special experiments to study the role of the first cervical dorsal root in transmission of facial sensory input to the nucleus caudalis.

At the end of the experiment, electrolytic lesions were made through the recording microelectrode *in situ* with dc current (20–50 microamperes) applied for 10 to 30 seconds. Animals were then sacrificed by administration of 100 per cent nitrous oxide. After formaldehyde fixation, the spinal cord was sectioned at 20-μm thickness, stained with cresyl violet, and electrode placement was established histologically.

Results

The nucleus caudalis of the trigeminal complex consists of two distinct regions, a rostral and a caudal portion, each with separate physiologic and pharmacologic properties. In the caudal portion, as the microelectrode was advanced dorso-ventrally along the tuberculum cinereum 5 to 10 mm caudal to the obex, cells responding only to high-threshold nociceptive cutaneous stimuli were discovered at depths of 800 to 1,600 μm from the cord dorsum. Their receptive fields were relatively wide over the ipsilateral face, with more intense responses as the center of the receptive field was stimulated. The activity of a central trigeminal nociceptor which responds only to high-threshold cutaneous stimuli applied to the ipsilateral face is shown in figure 1. This unit does not respond to low-threshold cutaneous stimuli such as bending hairs. Figure 2 (A) illustrates the firing frequency of a central trigeminal nociceptor and demonstrates a marked increase following needle stimulation applied to the ipsilateral face without response to hair stimulation alone. Nineteen trigeminal nociceptors were identified. Their locations are shown diagrammatically in figure 3.

In the three animals in which posterior roots of the first cervical spinal cord were present, it was found that section of the first dorsal filamentous spinal root altered neither spontaneous firing frequency nor modality of central trigeminal nociceptors. This may indicate that the first cervical dorsal root is not, in the cat, primarily involved in the transmission of data relating to noxious input to the face.

The rostral portion of the nucleus caudalis, on the other hand, contained nuclear aggregates responsive to low-threshold cutaneous stimuli applied to the ipsilateral face. These

cells were found in a microelectrode exploration from 2 mm caudal to the obex to the rostral border of the neural arch of the first cervical vertebra. No cells which responded only to noxious cutaneous stimuli were found in this region. Receptive fields of low-threshold units were widely represented, with the upper portion of the face represented ventrally and the lower portions of the face dorsally.[5, 9, 22] As shown in figure 2 (*B*), these cells responded briskly to hair stimulation, as well as to high-threshold cutaneous stimuli. Low-threshold cutaneous units were also found in the dorsal horn at a level beneath the neural arch of the first cervical spine somewhat dorsal to the central trigeminal nociceptors, suggesting a cytoarchitectonic organization somewhat similar to that of the lumbar spinal cord.[23, 24] The location of these low-threshold units is shown in figure 3. The number of such cells identified was 27.

In addition to the differences in physiologic properties, as noted, pharmacologic responses of units in the nucleus caudalis demonstrated a striking contrast. Of 19 central trigeminal nociceptors identified, ten had steady firing frequencies, with an average rate of 14/sec. The firing frequencies of these ten units were followed during a control study, during the administration of 75 per cent nitrous oxide in oxygen, and during recovery. As shown in figure 4, the spontaneous firing frequencies of the central trigeminal nociceptors were significantly suppressed by the administration of nitrous oxide, 31 per cent after 10 minutes and 35 per cent after 20 minutes of nitrous oxide administration. Firing frequencies returned to control values 5–20 minutes after cessation of nitrous oxide administration.

Among the 27 units identified which responded to low-threshold cutaneous stimuli applied to the ipsilateral face, 15 units had steady firing rates, with an average frequency of 16/sec. The firing frequencies of these low-threshold central mechanoreceptors were significantly facilitated by 75 per cent nitrous oxide, the average increases being 29 per cent after 10 minutes and 31 per cent after 20 minutes of nitrous oxide administration. They too returned to the control values 5 to 20 minutes after cessation of nitrous oxide administration.

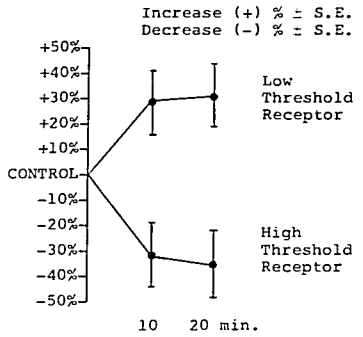

FIG. 4. Effects of 75 per cent nitrous oxide on the spontaneous firing frequency of a central trigeminal nociceptor and that of a low-threshold central mechanoreceptor. (Mean percentage change ±SE of spike trains from single cells.)

Electrolytic lesions made in the present study (figs. 5 and 6) indicate the region in which cells responding uniquely to nociceptive stimuli are located, the magnocellularis portion[25] of the first cervical segment extension of the nucleus caudalis, which is itself a direct extension of the dorsal horn of the cervical spinal cord. The region responsive to low-threshold cutaneous stimuli with a characteristic inverted somatotopy was the rostral portion of the nucleus caudalis, where projections from the mandibular, maxillary, and ophthalmic divisions of the trigeminal nerve have been shown to be arrayed dorso-ventrally.[19, 20, 22, 26]

Discussion

Numerous data indirectly suggesting the importance of the upper cervical cord in facial nociception derive from clinical,[10–13] phylogenetic,[14] embryologic,[15–17] and anatomic studies.[18, 19] Clinical findings are based on the observation that infarction of the territory of perfusion of the posterior inferior cerebellar artery results in loss of pain and temperature sensation in the ipsilateral face without the loss of tactile sensation.[10] A similar result is obtained in the surgical technique of treatment of trigeminal neuralgia by section of the

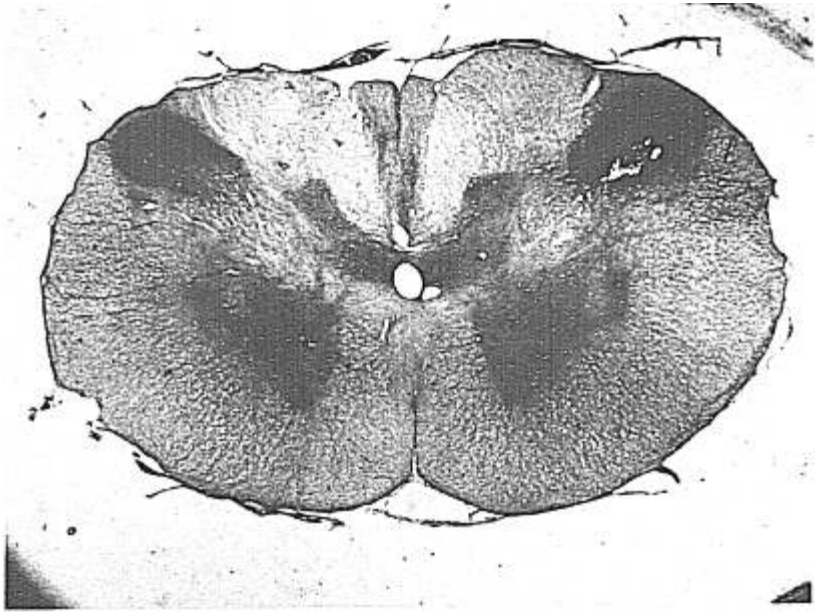

FIG. 5. A central trigeminal nociceptor located in the magnocellularis portion of the cervical extension of the nucleus caudalis. At the conclusion of unit recording, the electrolytic lesion was made through the recording microelectrode by passing dc current (30 microamperes) for 10 seconds.

spinal tract of the trigeminal nerve at the level of the inferior olive, proposed by Sjöqvist [11] and modified by Weinberger [12] and by Raney.[13]

Phylogenetic studies [14] have indicated that the nucleus caudalis is the first nucleus to differentiate in the trigeminal nuclear complex in vertebrates, and that it is very highly developed compared with other brain-stem nuclei of the trigeminal complex. At the time of its differentiation, a motor reflex is established through the contralateral upper cervical cord. These early differentiations and connections are found in all the vertebrate phyla. It might be argued that mechanisms developed in lower forms for dealing with high-intensity stimuli form the basis, in higher forms, for the structures requisite for experiencing pain.

Embryologic studies in man [15-17] show that the trigeminal tract extends to cervical levels and that the nucleus caudalis is continuous with the cervical dorsal horn. Secondary fibers arise earliest,[15] from the most caudal and phylogenetically oldest part of the spinal nucleus of the trigeminal complex.[15, 17] The upper cervical spinal cord thus contains a complete exteroceptive sensory pattern, sacral to cervical to trigeminal, in the fasciculus gracilis, fasciculus cuneatus, and descending spinal tract of the trigeminal and their corresponding nuclei.[9]

Studies of physiologic anatomy suggest that the caudalis portion of the trigeminal nuclear complex is related to nociception. Phenomena similar to those found in man following tran-

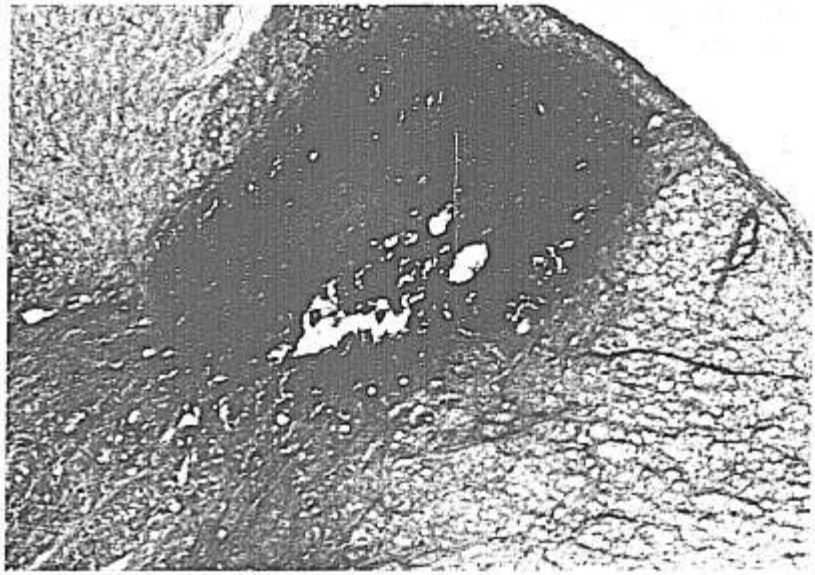

FIG. 6. High-power view of the lesion in figure 5.

section of the descending tract of the trigeminal nerve had previously been found in the cat by Gerard.[15] The explanation that this effect depended primarily upon small-fiber projection to the more caudal regions of the trigeminal nuclear complex was advanced.[11] Indeed, small fibers are found to preponderate in the electron microscopic studies.[19] The small fibers might be assumed to derive from nociceptors at the periphery supplied with small projection fibers. However, as first demonstrated by Wall and Taub,[9] it is probable that most small primary fibers found at caudal levels of the descending tract of the trigeminal nerve are derived from larger fibers at the periphery, which do not derive from nociceptors. The present study, while demonstrating the presence of central nociceptive cells, does not specify the origin of input to these cells, which remains to be determined.

Insofar as the mechanism of action of the central nociceptors of the caudalis nucleus is concerned, while it may be attractive to postulate a pure transmission mechanism for noxious stimuli to the face, mediated by a portion of cells in the nucleus caudalis, it is also of interest to consider the investigation of Scibetta and King,[27] in which dorsolateral medullotomy at the level of the obex decreased primary afferent hyperpolarization in fibers projecting to the nucleus oralis of the trigeminal, thus suggesting that a possible role for such nociceptive units is a permissive or "gating" one. Such a mechanism remains to be determined.

The evidence, primarily clinical, for a nociceptive function of cells in the region of the nucleus caudalis suggests that units uniquely responsive to noxious stimuli should be found there. More than a decade of study, however, produced no evidence of such cells,[5-9] with

the exception of a recent report by Mosso and Kruger.[21] The current study was prompted by two considerations, the first being the possibility that the apparent absence of such cells was related to anesthetic depression of their activity,[5-8] as seen, for example, in the spinal cord,[24] and the second being the realization that the study by Wall and Taub,[9] in which the "paradoxical" absence of central caudalis nociceptors was originally described, did not include an exploration of the upper cervical segments.[5-7, 9]

Thus the present study was accomplished in decerebrate cats, without basal narcosis, and was specifically directed to the more caudal regions of nucleus caudalis. While cells located more rostrally and dorsally within nucleus caudalis responded to low-threshold cutaneous stimuli, as previously reported,[5-9] in the present study, central trigeminal nociceptors have been found physiologically and demonstrated histologically in the more caudal regions of the nucleus caudalis in the magnocellularis zone.[25] This is the first such combined physiologic and histologic demonstration of central trigeminal nociceptors.

There are analogies between the nucleus caudalis of the trigeminal nerve and the lumbar spinal cord. Our results indicate that the central trigeminal nociceptors are located in the magnocellularis portion[25] of the nucleus caudalis and that cells located more dorsally respond to low-threshold cutaneous stimuli applied to the ipsilateral face. This localization may be compared to the laminar organization of the dorsal horn of the feline lumbar spinal cord, where central nociceptors were found in Rexed lamina 5[2-4] and low-threshold receptors in lamina 4.[23, 24] Mosso and Kruger[21] found central nociceptors in the marginal zone of the nucleus caudalis, a localization similar to the central nociceptors described by Christensen and Perl[28] for Rexed lamina 1 in the lumbar dorsal horn. The findings of Mosso and Kruger[21] await histologic confirmation.

The present study further demonstrates that the first posterior cervical root in the cat (occasionally found well developed) does not play a major role in the transmission of noxious stimuli from the face to the trigeminal nucleus caudalis. The receptive fields of the fibers in the posterior cervical root were not evaluated in this study.

A significant differential pharmacologic effect of nitrous oxide is present in the nucleus caudalis. Those cells classed as central trigeminal nociceptors are suppressed in their spontaneous activity, and the activity of those cells classed as low-threshold central mechanoreceptors is facilitated, by 75 per cent nitrous oxide in oxygen. A differential action is also present for cells in the dorsal horn of the feline lumbar spinal cord, where nitrous oxide selectively suppresses spontaneous activity in cells of Rexed lamina 5, responding to noxious stimuli, but has no significant effect on the spontaneous activity of cells in Rexed lamina 4, responding to low-threshold mechanical stimuli.[24]

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Neonatology

SURGICAL LESIONS AND RESPIRATORY DISTRESS This is a review of the common surgical lesions which cause respiratory distress in the neonate. Because of the relatively low incidence of these disorders, the hazard of undue delay in the diagnosis of these surgically correctable lesions is always present. Therefore, prompt diagnosis and immediate treatment are necessary for survival. The article is directed toward the radiologist who utilizes various techniques in attempts to diagnose the abnormalities which require surgical correction. The surgical disorders are divided into three categories: first, abnormalities of the extrathoracic airways, such as choanal atresia, pharyngeal airway obstruction by retrodisplacement of the tongue, congenital subglottic tracheal stenosis, and subglottic tracheal hemangioma. In the second group are included abnormalities of the intrathoracic major airway causing obstruction, including cystic hygroma, bronchial duplication cyst, esophageal atresia, and tracheoesophageal fistula. Group three consists of lesions causing compression of lung parenchyma, such as pneumoperitoneum. Diagnosis of these various lesions can be made by clinical as well as roentgenologic examination, provided an appropriate study is available. (*Schapiro, R. L., and Evans, E. T.: Surgical Disorders Causing Neonatal Respiratory Distress, Am. J. Roentgenol. Radium. Ther. Nucl. Med. 114: 305–321, 1972.*)