Central Connections of Trigeminal Primary Afferent Neurons: Topographical and Functional Considerations

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ABSTRACT: This article reviews literature relating to the central projection of primary afferent neurons of the trigeminal nerve. After a brief description of the major nuclei associated with the trigeminal nerve, the presentation reviews several early issues related to theories of trigeminal organization including modality and somatotopic representation. Recent studies directed toward further definition of central projection patterns of single nerve branches or nerves supplying specific oral and facial tissues are considered together with data from intraaxonal and intracellular studies that define the projection patterns of single fibers. A presentation of recent immuno-cytochemical data related to primary afferent fibers is described. Finally, several insights that recent studies shed on early theories of trigeminal input are assessed.

KEY WORDS: primary afferent, trigeminal, trigeminal ganglion, mesencephalic trigeminal nucleus, trigeminal sensory nuclei.

I. INTRODUCTION*

A. Overview

The primary goal of this article is to review the literature related to the central projections of primary afferent neurons of the trigeminal nerve. Specific somatotopic and functional patterns of the central termination of these neurons have been identified using a broad range of experimental approaches. As with most fields, progress in the understanding of the neurobiology of the trigeminal nerve and the somatosensory function of cranial nerves is closely linked to development of increasingly sophisticated experimental methods. General pathway tracing techniques have evolved to the point that specific observations of structure-function relationships at the single cell or subcellular level may be approached using intracellular and molecular techniques. Knowledge of the central distribution of trigeminal primary afferents provides the basis for critical studies of developmental pattern formation, regeneration subsequent to injury, and central plasticity in response to chronic changes in peripheral structures.

Trigeminal primary afferent neurons and their associated sensory receptors provide continual information necessary for the perception of changes in the external environment of the oral and facial regions. Of clinical significance, these neurons mediate a variety of pain states including dental pain, trigeminal neuralgia, temporomandibular-joint pain, muscle pain, and headache. Oral stereognosis (Landt, 1983) and kinesthesia (Morimoto, 1983) are examples of other sensory phenomena mediated by somatosensory fibers of the trigeminal nerve. Neurons and receptors that provide these signals to the central nervous sys-
tem may be important in the process of adapting to altered patterns of mastication in the course of orthodontic treatment. Similarly, factors such as masticatory efficiency and overall patient satisfaction subsequent to dental procedures are significantly influenced by this neural input (Landt, 1983).

In addition to providing general somatosensory information from orofacial structures, trigeminal primary afferent neurons are involved in numerous behavioral responses involving sensorimotor integration at all levels of the neuraxis. Their role in the initiation of relatively simple orofacial reflexes such as the jaw-opening reflex, which is somewhat comparable to the spinal cord flexor withdrawal reflex (Mason et al., 1985), and the jaw-closing reflex, which is comparable to the classic spinal cord myotatic reflex, is well documented. Early studies of trigeminal reflexes led to theories of mastication that involved the coordination of simple opening reflexes and rebound jaw closure (Sherrington, 1917). Such theories have undergone substantial modification since the observations of Sherrington and current evidence favors the existence of pattern generators that are responsible for fundamental patterns of mastication and swallowing. Even though the basic movement patterns may be centrally generated, primary afferent neurons play a role in modulation of the pattern generators (Rossignol et al., 1988; Lund, 1991). Trigeminal afferent fibers also contribute to other types of sensorimotor integration such as the coordination of the head and neck movements with other parts of the body during complex movement patterns.

B. Central Distribution of Trigeminal Primary Afferent Fibers, General

The majority of the primary afferent neurons related to cranial somatosensory function are components of the trigeminal nerve. Fibers of the trigeminal nerve originate from somata in the trigeminal (gasserian or semilunar) ganglion or in the trigeminal mesencephalic nucleus. Smaller contributions to the spinal trigeminal nuclei originate from the ganglia of the facial (VII), glossopharyngeal (IX), and vagus (X) nerves.

The central processes of trigeminal ganglion cells enter the pons via the sensory root of the trigeminal nerve and form a compact descending bundle known as the spinal (descending) tract of the trigeminal nerve. This tract, which is located in the dorsolateral region of the brain stem in most species, extends from middle pons to the second or third cervical spinal cord segment where the caudalmost fibers overlap with Lissauer’s tract (dorsolateral fasciculus). The spinal tract is somatotopically organized such that the fibers of cells innervating the ipsilateral mandibular division are most dorsally situated, the maxillary fibers are in the middle, and the ophthalmic fibers are in the most ventral part of the tract (i.e., an inverted hemiface pattern). This basic organization has been known for many years and has been confirmed by clinical observation and numerous laboratory experiments (for comprehensive reviews of early literature see Humphrey, 1969). Contributions from cranial nerves VII, IX, and X, which enter the brain stem at their respective levels in the medulla, take a position just dorsal to the fibers of the mandibular division. This somatotopic pattern persists caudally into the upper cervical spinal cord where the mandibular fibers shift medially and the ophthalmic fibers shift laterally.

Although most early accounts agree regarding the somatotopy of fibers in the spinal trigeminal tract, there is less agreement regarding the caudal extent of trigeminal representation in the upper cervical spinal cord. Evoked potential studies suggest that fibers of the mandibular division end mainly near the obex, whereas the evoked potentials from stimulation of the maxillary and ophthalmic divisions have been recorded as far caudal as the C-2 spinal cord segment. Early degeneration studies using techniques for staining degenerating myelin (e.g., the Marchi method), but not unmyelinated degenerating fibers, probably contributed to this controversy. Kerr (1963) made lesions in the trigeminal ganglion (stereotaxically) and surgically transected each of the trigeminal nerve divisions in cats and monkeys. Using the Nauta-Gygax technique, which stains degenerating axons of all diameters, Kerr (1963) verified the basic somatotopic pattern in the spinal trigeminal tract and proved that
all three divisions of the trigeminal nerve are represented as far caudally as the upper half of the second cervical spinal cord segment.

Although each division of the trigeminal nerve is represented throughout the rostrocaudal extent of the trigeminal nuclei, there is considerable evidence that the extent of representation for specific peripheral structures may vary among the subnuclei (Kruger, 1979). Marfurt (1981) performed one of the first anatomical studies that systematically evaluated the overall central representation of large numbers of trigeminal afferents. He transected the peripheral trigeminal nerve branches and surgically excised the cornea and treated them with horseradish peroxidase (HRP). The adequate survival time to permit complete transganglionic transport of this axonal tracer enabled Marfurt to describe the terminal projection sites for corneal afferent and the afferents in single nerve branches. This study revealed that each area of the cat’s head and face was represented as a longitudinal column that ran from the middle pons to the upper segments of the cervical spinal cord and that these columns differed from each other in size, shape, and precise rostrocaudal extent. The relative amount of transganglionic labeling indicated that mandibular structures innervated by the inferior alveolar nerve were uniformly represented, whereas nerves innervating ophthalmic (cornea and supraorbital n.), maxillary (infraorbital n.), and cutaneous structures on the anterior face (mental n.) were not uniformly represented. Later studies in the cat by Shigenaga et al. (1986a,b) labeled additional nerve branches and compared the distribution of primary afferent fibers from intraoral and facial regions in the trigeminal nuclei. The studies by Shigenaga et al. (1986a,b) described complex patterns of representation of intraoral structures in both the rostral and caudal parts of the trigeminal nuclei. They also documented an onion-skin-like (concentric) pattern of termination from facial cutaneous regions in layers I and II of the MDH, thus reinforcing the basic organization of the pattern described by Dejerine (1914). Although there are some differences in the specific details of central representation of primary afferent fibers as determined by transganglionic studies and the electrophysiological experiments by Eisenman et al. (1963) and Kruger and Michel (1962a,b,c), existing evidence favors the concept that all facial regions are represented in rostrocaudally oriented columns throughout the trigeminal nuclei, but some structures have greater representation in certain subnuclei. Regional differences in central representation and occasional discontinuities possibly result from differences in peripheral innervation density and afferent modality representation within certain tissues, phylogenetic differences among species, and technical factors.

Most of the central processes of trigeminal ganglion cells enter the brain stem at their respective levels and bifurcate into ascending and descending branches. However, it has been known since 1926 (Windle, 1926a,b) that some percentage of small-diameter primary afferent fibers enter the pons via the sensory root of the trigeminal nerve, turn caudally in the spinal tract without branching, and terminate in more caudal regions of the spinal trigeminal nucleus. Even though many of the small-myelinated (A-β) and unmyelinated (C) fibers proceed to the caudal parts of the trigeminal sensory nuclei without giving ascending branches, they do give off collaterals en route. There is some evidence (Shigenaga et al., 1986a) that more rostral collaterals of small diameter fibers may provide the afferent limb for trigeminal reflexes, whereas more caudal collaterals terminate on cells in spinal trigeminal nuclei that will transmit nociceptive information to the reticular formation, the contralateral thalamus, and other central structures. Larger diameter fibers may follow a similar distribution pattern for distribution of certain types of mechanoreceptive information. Patterns of fiber distribution have been observed in recent intraxonal labeling studies of large myelinated primary afferent neurons (Hayashi, 1981; Tsuru et al., 1989) and it is clear that some descend without bifurcation, whereas others bifurcate, giving rise to ascending and descending branches. Tsuru et al. (1989) found that the ratio of descending nonbifurcating to bifurcating fibers was about the same for primary afferents located in the periodontal ligament and the tooth pulp. Finally, some portion of the large-diameter fibers ascend without branching to terminate in the principal sen-
sory nucleus of the trigeminal nerve (Windle, 1926a,b). A schematic diagram showing some options for the distribution of the central processes of ganglion cells in shown in Figure 1.

![Schematic Diagram of Nuclei](image)

**FIGURE 1.** This schematic diagram, representing a dorsal view of the brain stem, shows the general pattern of central distribution for large-, medium-, and small-diameter fibers of trigeminal ganglion cells (TG) into the spinal trigeminal nucleus on the right. Note the decussating fiber caudal to the obex. Major subdivisions of the spinal trigeminal nucleus are shown on the left including the principal sensory nucleus V₃, subnucleus oralis (Vₒ), subnucleus interpolaris (Vᵢ), and subnucleus caudalis (Vₑ). Subnucleus caudalis overlaps with the second cervical spinal cord segment (C-2).

In addition to trigeminal ganglion neurons, the trigeminal nerve contains a population of primary afferent fibers whose cell bodies are located within the central nervous system. This group of cells is referred to as the mesencephalic trigeminal nucleus or the mesencephalic nucleus of the trigeminal nerve (V₃mes) because it extends from the pons to the rostral midbrain. The peripheral processes of these cells innervate mas-
ticatory muscle spindles and periodontal receptors (Capra and Wax, 1989). Originally, the emphasis on functional studies of this nucleus was placed solely on its role in the jaw closing reflex that involved monosynaptic connections from V₃mes spindle afferents onto cells in the trigeminal motor nucleus (V₃mot; Szentágothai, 1948). This emphasis dominated research for years, even though it was known that a caudally projecting bundle originating from these cells descended into the medulla (Probst, 1899). The central distribution of the V₃mes cells (Capra and Wax, 1989; Luschei, 1987) and patterns of collateral distribution of different types of muscle spindle afferents and periodontal afferents have become the focus of renewed interest (Appenteng _et al._, 1985; Dessem _et al._, 1988; Dessem and Taylor, 1989a; Shigenaga _et al._, 1989, 1990a). Recent data regarding the central projections of these cells and other features of this nucleus will be discussed.

**C. Trigeminal Sensory Nuclei**

An account of the central projections of the nerves that innervate oral and facial tissues necessitates some treatment of the anatomical organization of the nuclear groups that receive this innervation. A large variety of species have been examined with respect to the morphology of the trigeminal nuclei, but the majority of connectivity and neurophysiological studies germane to this review have been conducted in rats, cats, rabbits, and subhuman primates.

Early descriptions of the trigeminal nuclei in rodents are provided by Rámón y Cajal (1909), Lorente de Nó (1922), and Aström (1953). The location and cytoarchitecture of the trigeminal nuclei are generally well described in cats by Taber (1961) and Berman (1968). The description of the trigeminal nuclei in rabbits provided by Meeser and Olszewski (1949) was adapted by Eisenman _et al._ (1963) to describe the more rostral trigeminal subnuclei in cats. Perhaps the most widely cited description of the anatomical organization of spinal trigeminal nucleus was published by Olszewski (1950). Based on material from human and subhuman primates, Ol-
szewski’s findings are broadly applicable to most species.

The brain-stem nuclei, classically recognized as major recipients of trigeminal primary afferent input include the principal nucleus (Vp) and the spinal trigeminal nucleus. It has become common usage to refer to these nuclei collectively as the trigeminal brain-stem nuclear complex (Marfurt, 1981) or as the trigeminal sensory nuclear complex (Shigenaga et al., 1986a). The trigeminal mesencephalic nucleus is usually excluded from this nomenclature because it is composed primarily, if not exclusively, of primary afferent neurons. A number of ultrastructural studies that focus on specific regions of the spinal trigeminal nuclei (e.g., Gobel et al., 1977, 1981; Gobel and Dubner, 1969; Falls, 1986a,b; Phelan and Falls, 1989a,b) have added to the morphological descriptions of these subnuclei.

The following description of the trigeminal sensory nuclei is offered with the caution that readers should consult more detailed references for the cytoarchitectural, functional, and semantic differences related to a particular species. Although it is based primarily on organization in mammals, the trigeminal system is quite consistently represented throughout phylogeny (Crosby and Yoss, 1954) and many insights into the organization of the trigeminal system were developed from comparative studies in lower vertebrates (Ariëns-Kappers et al., 1967).

1. Spinal Nucleus of the Trigeminal Nerve

The spinal nucleus of the trigeminal nerve is located deep to the spinal tract. Three major cytoarchitectonic subdivisions of this nucleus are generally recognized along its rostrocaudal axis. The most caudal of the subdivisions is the subnucleus caudalis (Vc), which extends from C2 or C3 caudally to the obex rostrally. This part of the spinal trigeminal nucleus overlaps with the dorsal horn of the cervical spinal cord. The subnucleus interpolaris (Vs) extend from the obex caudally to the caudal pole of the facial motor nucleus. The most rostral subdivision is the subnucleus oralis (V or). Also referred to as subnucleus rostralis (Crosby and Yoss, 1954), this region extends from the caudal pole of the facial motor nucleus to the caudal end of V mot. The orientation of these nuclei in the longitudinal plane is shown schematically in Figure 1, and the relative positions of the major components of the cat trigeminal nuclear complex and related structures are shown in Figure 2.

a. Subnucleus Caudalis

There are obvious similarities in the cytoarchitectural and the synaptic organization between Vp and the dorsal horn of the spinal cord. Olszewski (1950) described this area as consisting of outer marginal, intermediate gelatinous, and inner magnocellular layers. Its similarity to the dorsal horn has resulted in subdivision of this segment of the trigeminal nuclei using either spinal cord laminae designation of Rexed (1952, 1954) or a similar pattern described by Gobel et al. (1977, 1981). The latter authors describe this region as the medullary dorsal horn (MDH) and provide specific ultrastructural rationale for subdivisions of this part of the trigeminal system. The term MDH is used regularly when describing precise functional or morphological relationships in this part of the trigeminal complex, whereas Vp is used when describing the general gross organization of the sensory nuclei.

Layer I of the MDH as described by Gobel et al. (1981) corresponds to the marginal layer described by Olszewski (1950). Olszewski (1950) referred to an area comprising both layers II and III as the substantia gelatinosa in the medulla while Rexed (1952, 1954) considered only layer II as the gelatinosa layer. The original description by Gobel et al. (1977) recognizes layers II and III as separate structures without designating a specific homology with the gelatinosa layer. However, a subsequent description divides layer II into a and b subdivisions (Gobel et al., 1981; Figure 3). This division was in better agreement with the spinal cord pattern proposed by Rexed (1952, 1954) and comprises most of the substantia gelatinosa. A concise presentation of some of the use of the nomenclature regarding this region is presented by Gobel et al. (1981).
FIGURE 2. Diagrams of representative transverse sections of the brain stem in cat to show the relative position of the spinal trigeminal nuclei and the spinal trigeminal tract. The inset regions are enlarged on the right. (a) The dorsal (Vpd) and ventral (Vr) divisions of the principal sensory nucleus (Vp) are located in the pons at the level of the trigeminal motor nucleus (Vo). This is also the level at which the supratrigeminal (Vr) and intertrigeminal (Vr) nuclei are located. (b) The ventral part of Vr overlaps with pars γ of subnucleus oralis (Vo) in the upper medulla at the level of the genu and exiting root fibers of the facial nerve. (c,d) Subnucleus interpolaris Vr is located in the medulla from a level just caudal to the facial motor nucleus. The spinal tract of the trigeminal nerve (ST) contains components of the interstitial system of neurons (SVT): arrows). The parvocellular reticular formation (Vpd) is located medial to the spinal trigeminal nucleus. (e) The laminar organization of the subnucleus caudalis (Vc) was described by Gobel et al. (1977, 1981) and led to use of the term medullary dorsal horn (MDH) to describe the connections of this region.
There is considerable convergence of orofacial information onto cells in the intermediate layers (III and IV). This part of the MDH contains many interneurons involved in intranuclear connections within the MDH as well as between the MDH and the more rostral subnuclei. Layers V and VI make up the neck of the MDH. Trigeminothalamic cells, which are located primarily in layers I, V, and VI, are thought to provide the anatomic and physiologic substrate for the sensory-discriminative aspects of pain and temperature perception in the facial region (Dubner et al., 1978).

b. **Subnucleus Interpolaris**

The subnucleus interpolaris (V) bridges the area between the subnucleus oralis V₀ and the V₁. From a cytoarchitectural perspective, the boundary between the V₀ and V₁ occurs rather gradually and it is marked by a short transitional region located near the obex. This transitional area, which has been termed the “nonlaminar portion of pars caudalis” (Marfurt, 1981), contains interstitial cell clusters scattered among the spinal tract that are functionally related to the MDH and other nuclei in this region (Phelan and Falls, 1989b). Both the medial and rostral boundaries between V₁ are fairly subtle when viewed under the light microscope. This is particularly true of its relationship medially with the subjacent reticular formation. Phelan and Falls (1989a) recently reviewed studies of structural and functional aspects of V₁ in several species. Some descriptions of this nucleus indicate that it consists of a rather homogeneous distribution of neurons of various sizes (Olszewski, 1950; Crosby and Yoss, 1954), whereas others suggest that there are regions of cellular specialization within the nucleus (Åström, 1953; Torvik, 1956).

It is likely that apparent discrepancies in the accounts of V₁ morphology are due to phylogenetic variables. The vibrissae are well developed in rodents and have heavy central representation in V₁. Consistent with this suggestion is the fact...
that similar tendencies toward nuclear diversity have been reported in the V of cats whose vibrissae pads are also well developed (Somers and Panneton, 1984), whereas other species lacking well-developed mystacial vibrissae may show less specialization in V.

Phelan and Falls (1989a) describe six cytoarchitecturally distinct regions in rat V. Of these morphologically defined regions, several receive primary afferent inputs from different orofacial regions. The dorsolateral region receives input from the auriculotemporal nerve (Jacquin et al., 1983). The ventrolateral region receives input from vibrissae and other maxillary and ophthalmic structures. The subdivisions of V are also predicted on regional differences in their efferent connections. Projections to thalamus, cerebellum (Patrick and Haines, 1982), and spinal cord (Hayashi et al., 1984) have all been identified in specific regions of V. Although homologies between V and spinal cord gray-matter structures have been considered, its diverse organization has complicated this assignment. It has been suggested that parts of this nucleus have properties of cells in the dorsal column nuclei (Shigenaga et al., 1986a). Others have considered that this region may correspond roughly to the cranial homolog of the spinocerebellar system. Although trigeminocerebellar connections have been described in V, they are not extensive nor exclusive to V (Kruger, 1979).

c. Subnucleus Oralis

The most rostral component of the spinal trigeminal nucleus is subnucleus oralis (V). It consists of a heterogeneous population of multipolar neurons that are generally described as a mixture of large and small neurons. Eisenmann et al. (1963) applied the term subnucleus oralis to describe all of the trigeminal nucleus between the principal sensory nucleus and V, which was then divided into pars α, β, and γ. It appears that V, as described by most workers, corresponds to subnucleus oralis pars γ and perhaps part of pars β, whereas pars α seems to correspond to V. Extracellular recordings in V pars γ revealed the usual inverted face somatotopic pattern. In addition, a medial to lateral topography was identified (Eisenman et al., 1963). Intraoral structures were represented more medially, whereas vibrissae and more posterior facial structures were represented laterally. The rodent V has been subdivided into a number of different regions based on light microscopic and ultrastructural features of this region (Falls, 1984, 1985, 1986a,b, 1987). Recent data show that some of these regions contain significant numbers of premotor neurons (Westberg and Olsson, 1991; Olsson and Westberg, 1991). In addition to local circuit neurons, parts of V contain neurons that project to contralateral thalamus, ipsilateral cerebellum, and ipsilateral spinal cord (Jacquin and Rhoades, 1990).

2. Principal Sensory Nucleus

The principal sensory (V) nucleus has also been termed the chief or main sensory nucleus. In the 5th edition of Nomina Anatomica (Nomina Anatomica, 5th edition. (1983): Williams & Wilkins, Baltimore.), the term “pontine nucleus” is suggested because of its position in the pons rather than using adjectives such as chief or principal that may be misleading. However, the majority of recent literature favors V. It is located dorsal and lateral to V mot and receives the ascending branches of the trigeminal primary afferent fibers as well as some nonbifurcating fibers. For the most part, these fibers are large diameter and contribute to perception of the most discriminative types of sensation. Much of the projection to V is from ganglion cells that innervate intraoral structures. The dorsal and medial parts of the nucleus consist of densely packed populations of cytoarchitecturally homogeneous cells. In cats, V consists of distinct dorsal (Vd) and ventral (Vv) parts (Shigenaga et al., 1986b). The ventral part overlaps with parts γ of V. Traditionally, the V has been considered homologous in function to the dorsal column nuclei (Kruger, 1979). However, this homology has been questioned for several reasons, one being the rather unique organization of the projection to V from the oral cavity, including the dental pulp (Marfurt and Turner, 1984; Shigenaga et al., 1986b,c).
3. Mesencephalic Trigeminal Nucleus

The mesencephalic trigeminal nucleus (Vmes) is often described as a narrow band of pseudo-unipolar cells extending from the pons to the midbrain. Recent anatomical evidence, however, has questioned this definition based solely on pseudo-unipolar cell morphology. Multipolar cells are found scattered among the pseudo-unipolar cells after the peripheral application of neuronal tracers to the alveolar nerves, nerves to the muscles of mastication, and the tissues they innervate (Capra et al., 1984; Gottlieb et al., 1984; Luo et al., 1991; Nomura et al., 1985; Nomura and Mizuno, 1985; Shigenaga et al., 1988b; Walberg, 1984). Shigenaga et al. (1990a) have labeled some multipolar cells that were responsive to jaw-muscle stretch and had brain-stem projections similar to the pseudo-unipolar cells. Luo et al. (1991) have also observed multipolar cells whose cell bodies were located among the pseudounipolar Vmes cells and activated at rather long latencies by stimulation of the masseter nerve. In contrast to the results of Shigenaga et al. (1990), Luo et al. (1991) found a different central distribution for the multipolar cells, including projections to the periaqueductal gray, midbrain reticular formation, locus coerules, nucleus subcoeruleus, and medial parabrachial nucleus. These studies advocate expanding the definition of Vmes to encompass all first-order trigeminal primary afferents whose cell bodies, regardless of cell morphology, are located rostrally, surrounding the periaqueductal gray, and caudally, adjacent to the lateral edge of the floor of the fourth ventricle.

The pseudo-unipolar cells are often found in small clusters. In both the cat and rat, individual clusters have been shown to contain afferents from different muscles of mastication (Rokx et al., 1988) and from the periodontium (Gottlieb et al., 1984; Capra et al., 1984; Capra and Wax, 1989). Cells within these clusters are closely opposed and allow electrotonic coupling between Vmes cells (Baker and Linas, 1971; Hinrichsen, 1970). Several functional hypotheses have been proposed for this electrotonic coupling including synchronization (Alley, 1973; Hinrichsen, 1968, 1970) and a rapid type of inhibition (Taylor et al., 1978).

a. Synapses on Mesencephalic Trigeminal Neurons

Light microscopic techniques have revealed axonal swellings and terminal boutons have been reported in close association with Vmes cells in mice, rats, hamsters, guinea pigs, and cats. Further analysis at the electron microscopic level has demonstrated the presence of typical synaptic structures on these cells (Alley, 1973; Copray et al., 1990; Hinrichsen and Larramendi, 1970; Inagaki et al., 1987; Imamoto and Shimizu, 1970; Nomura et al., 1985) with at least two different morphological types of synaptic boutons (Alley, 1973; Imamoto and Shimizu, 1970). The neurotransmitters released at the synapses onto Vmes cells remain problematic. Adenosine decarboxylase, dopamine, enkephalin, histidine decarboxylase, serotonin and substance P have all been localized in the terminals surrounding Vmes cells (Copray et al., 1990, 1991; Inagaki et al., 1987; Nagy et al., 1986). Physiological studies, however, have not yielded further insight into the transmitters at this site (De Montigny and Lund, 1980; Henderson et al., 1982; Regenold et al., 1988).

4. Other Nuclei

Trigeminal afferents have numerous targets other than the classically defined sensory nuclei of the trigeminal complex (Marfurt and Rajchert, 1991). The role of several of these projections in oral and facial functions is not well understood at present. However, functional and regional considerations justify the inclusion of several regions in this review. These include the supratrigeminal and intertrigeminal nuclei that are located in the pons in proximity to the motor nucleus of the trigeminal nerve, the reticular formation immediately subjacent to the spinal trigeminal nucleus, and the interstitial cells that are insinuated in clusters extending along the spinal tract of the trigeminal nerve from the caudal pons to the spinomedullary transition region. In addition to these regions, trigeminal primary afferents have been shown to project directly to the cerebellum, the nucleus solitarius, the vestibular nucleus, the re-
ticular formation, the cuneate nucleus, the hypoglossal nucleus, and lower cervical spinal cord (Pfaller and Arvidsson, 1988; Marfurt and Rajchert, 1991; Segade et al., 1990; Åström, 1953; Torvik, 1956).

a. Supratrigeminal and Intertrigeminal Nuclei

Although many studies have reported projections to the supratrigeminal nucleus or region, the precise definition of this nucleus is inconsistent. Lorente de Nó (1922) originally described the supratrigeminal nucleus (Vsup) in the mouse as “above the dorsolateral region of the principal motor nucleus and proximal to the sensory nucleus. Ventrally (this nucleus) touches the motor nucleus, dorsally it is limited by the radiation to the locus, on the outside it is limited by the sensory nucleus of the trigeminal and on the inside it is lost in the reticular substance.” Despite this definition, some have expanded Vsup to include the entire region dorsal to Vmot (Paxinos and Watson, 1986). Figure 4 shows the relationship between Vsup and the surrounding trigeminal nuclei in the mouse and cat.

In the cat, there is lack of agreement regarding the boundaries of the Vsup. Shigenaga et al. (1990a) described a nucleus that was dorsal to, but separate from, Vmot. This differs from the description in the mouse by Lorente de Nó (1922) who states that Vsup “touches the motor nucleus.” Although this nucleus was recognized by Torvik (1957), several workers regarded scattered cells in the region between Vp and Vmes as part of Vp (Kruger and Michel, 1962a; Berman, 1968). Using single-unit recording techniques, Jerge (1963b) described unit responses that he attributed to the Vsup. It is quite possible that these responses were actually recorded from pars γ of Vp because they are similar to those reported by Eisenman et al. (1963). Furthermore, the transverse sections Jerge uses to illustrate his electrode recording sites also corresponds to the level of Vp described by Eisenman et al. (1963). Landgren and Olsson (1976) provided anatomical and physiological evidence supporting the definition of Vsup in the cat (see Figure 4). Recent evidence (Westberg and Olsson, 1991; Olsson and Westberg, 1991) demonstrates the presence of premotor neurons in pars γ of Vp with properties that have been attributed to units in Vsup. It may be entirely possible that the region described as Vsup in cats is an extension of the neuropil and scattered cells from pars γ of Vp. Berman (1968) does not recognize a separate Vsup and considers the entire region dorsal to the motor nucleus as part of Vp.

The intertrigeminal nucleus (Vint) as described by Lorente de Nó (1922) consists of a group of multipolar cells located ventrally between the trigeminal principal sensory nucleus Vmot. Studies by Landgren and Olsson (1976) confirm a similar, though more extensive, location for this nucleus in the cat. Direct projections from Vmes muscle afferents to this nucleus have been described in the rat (Luo et al., 1991) and cat (Shigenaga et al., 1988b, 1990a), though other studies did not confirm this projection (Dessem and Taylor, 1989a).

b. Interstitial System of the Spinal Trigeminal Tract

The transition between Vc and Vi in cats begins immediately caudal to the obex and has been described as the nonlaminar zone of the MDH by Marfurt (1981). This region contains cell clusters embedded in the spinal tract of the trigeminal nerve (see Figure 2). In rodents, clusters of neurons scattered along the spinal tract of the trigeminal nerve near the level of the obex and extending rostrally were termed interstitial neurons by Rámón y Cajal (1909). In cats, scattered islands of cells are found as far rostrally as Vp. The extensive nomenclature that has developed in various descriptions of these cell clusters has been reviewed thoroughly by Phelan and Falls (1989b). They referred to these cells collectively as the interstitial system of the spinal trigeminal tract (SVTint). Intraxonal studies have shown that collaterals of trigeminal nociceptive fibers project to both the interstitial cells and to the MDH (Marfurt, 1981; Shults and Light, 1987). This pattern of fiber projection has led to suggestions that the interstitial cells represent a rostral extension of the MDH. Recently, Hayashi and Tabata (1989a, 1991) showed that inter-
These diagrams illustrate the relationships between the trigeminal motor nucleus (V_mn), the principal sensory nucleus (V_s), the mesencephalic nucleus (V_me), the supratrigeminal nucleus (V_spt), and the intertrigeminal nucleus (V_it), in the mouse (upper left) and cat (lower left). The inset on the upper right is a schematic drawing of Golgi-stained material illustrating the relationships between the neurites of V_spt and V_mn. These drawings are adapted from the original work by Lorente de Nó (1922) (mouse) and Landgren and Olsson (1976) (cat).

Interstitial cells project to the mesencephalic parabrachial area in cats. Most of these cells receive nociceptive inputs from orofacial structures. However, it has been shown that groups of interstitial neurons are heterogeneous with respect to their cytoarchitecture and their central connections. For example, some groups of interstitial cells appear to be involved in the relay of information to the thalamus, whereas others have cerebellar projections (Phelan and Falls, 1989b).
though some portion of the interstitial cells represents a rostral continuation of layers I and II of the MDH (Shults and Light, 1987) the area seems to be more complexly organized. It appears to represent "fragmentation" of more than one functionally discrete central structure.

c. Parvocellular Reticular Formation

The region immediately medial to the spinal trigeminal nucleus consists of small neurons that receive input from trigeminal ganglion cells and Vₘₚ (Ruggerio et al., 1982). The cytoarchitectural boundaries of this area are poorly delineated, but it extends throughout the medulla and lower pons. A significant number of these cells are interneurons that project onto trigeminal, facial, and hypoglossal motoneurons (Holstege et al., 1977), whereas others project onto Vₘₚ and cells in the supratrigeminal region (Jüch and Rokx, 1988). Berman (1968) identifies an external division of the lateral reticular formation in the medulla of cats that corresponds to the parvo-cellular division of the lateral reticular nucleus described by Ránán y Cajal (1909) in the mouse. This region has been described variously by different authors and has not been characterized completely. Because the prevailing cytoarchitecture of this area consists of small cells, the term "parvocellular reticular formation" (PCRIF) has been used to designate this region (see Figure 2). Reticular areas of the MDH are scattered throughout layers V through VIII, and it has been suggested that specific layers should not be used to define specific reticular formation structures (Gobel et al., 1977). It is likely that the PCRIF continues to overlap caudally with spinal cord reticular areas. Functional analysis may show that some of these cells have similar properties to neurons described in the supratrigeminal region.

An analysis of the literature regarding the distribution of trigeminal interneurons suggests the presence of species-dependent regional variations in the Vₚₚ, that permit identification of smaller subdivisions along its rostrocaudal course, for example, the nucleus of Probst, located medial to Vₚ, in rats (Matesz, 1981). A relatively new term is appearing in current literature. Several authors refer to a juxtatrigrigeminal nucleus or region. As used by Luo et al. (1991), it seems that this region is somewhat limited to the area medial to trigeminal motoneurons in the rat. Further study of the morphological distribution of trigeminal interneurons is warranted. It is hoped that descriptions of morphologically or functionally discrete areas will be named with caution.

II. REPRESENTATION OF SPECIFIC PERIPHERAL STRUCTURES AND RECEPTORS

A. Cutaneous

1. Facial Skin and Nonvibrissae Hair

Current knowledge about the central representation of facial cutaneous structures is derived from physiological studies of central neurons (Dubner et al., 1978; Sessle et al., 1986), axonal labeling reports on the central distribution of cutaneous nerves (Marfurt, 1981; Shigenaga et al., 1986a, b, 1990b) or peripheral structures (Capra, 1985; Chiego et al., 1980; Marfurt and Turner, 1984), and intraaxonal labeling studies on the distribution of single physiologically identified primary afferent fibers (Hayashi, 1981, 1985a, b; Hayashi et al., 1984).

Hayashi injected HRP intraaxionally into physiologically identified, large, myelinated afferents in rats (Hayashi, 1981, 1985a) and in cats (Hayashi, 1985b). Using physiological criteria (e.g., Zucker and Welker, 1969; Gottschaldt et al., 1973), vibrissae, guard hair, and slowly adapting type I afferents were studied in both species. In addition, (D) hair receptors and Aδ high-threshold cutaneous mechanoreceptors were identified and labeled in cats (Hayashi, 1985a). In the rodent studies (Hayashi, 1981, 1985a), a regular morphological differentiation was observed in the terminal arbors of low-threshold afferents originating from progressively more caudal collateral branches. These were divided into rostral-type collaterals, caudalis-type collaterals, and spinal dorsal horn-type collaterals. Although regional differences were observed within each fiber, the overall morphology of the functionally different types of large, myelinated af-
ferent fibers was similar. The rostrocaudal differentiation was much more pronounced than the morphological differences observed between the arbors of spinal cutaneous afferents (Brown, 1981). In periobex regions, collaterals of trigeminal afferent fibers formed terminal arbors in the outer part of spinal nucleus. In rostral MDH, they terminated in layer V, whereas in caudal MDH and cervical spinal cord, they terminated mainly in layers III and IV. The occurrence of a shift in projections to different layers is not typical of the pattern seen with spinal ganglion cells. The laminar distribution of terminals from large, myelinated fibers to MDH in rats (Hayashi, 1985a) and cats (Hayashi, 1985b) differed from that of functionally similar spinal cord primary afferents (Brown, 1981). Although it was suggested that this might be due to the particular criteria for determining cytoarchitectural boundaries, it is likely that the differences reflect variations in local circuitry. In contrast to the distribution of the low-threshold afferents, terminal arbors of high-threshold fibers from cutaneous structures were sparsely distributed to superficial regions of V1 and more heavily to layers I and IIa of MDH. The distribution to the outer layers of the MDH was similar to that of high-threshold afferent fibers in the spinal cord dorsal horn. In contrast to spinal high-threshold afferents, trigeminal fibers did not project to layer V. Single fiber studies in the cat, therefore, revealed significant differences in the terminal arbor morphology between low- and high-threshold afferents (Hayashi, 1985b). Another important finding of this report was confirmation at the single fiber level that trigeminal nociceptive afferents terminated in V1. A schematic diagram of the central pattern of distribution of low- and high-threshold afferents, and the appearance of their terminal arbors, modified from two figures by Hayashi, summarize the relationships described above (Figure 5).

2. Vibrissae

Transganglionic transport studies following HRP applications to the infraorbital nerve revealed an unequal rostrocaudal vibrissae representation in cats. Although infraorbital nerve fibers project to all regions of the spinal trigeminal nucleus, relative to V1, the representation is reduced at V0 and rostral V1 (Marfurt, 1981). These studies provide an overall perspective in which the analysis of single fibers by intraxonal recording and labeling studies may be compared.

The central distribution of single vibrissae afferents has been extensively documented in rodents (Jacquin et al., 1984, 1986; Hayashi, 1981, 1985a) and terminals of single vibrissae afferents have been observed in all parts of the spinal trigeminal nucleus. In the first of a series of articles related to structure-function relationships in rat V1, Jacquin et al. (1986) identified three classes of slowly adapting afferents and two classes of rapidly adapting afferents in V1, using criteria based on their own observations and those by Gottschaldt et al. (1973). Individual fibers gave rise to as many as 10 collateral branches that ran perpendicular to the spinal tract and ended in "densely packed circumscribed terminal arbors". Although arbors from adjacent collaterals often overlapped and formed large ovoid masses the morphology of each was similar, regardless of their physiological class or the type of vibrissae innervated (e.g., mystacial vs. supraorbital). The topographic pattern within the brain-stem trigeminal nuclei was very distinct. Dorsal row vibrissae fibers innervate ventral interpari, whereas fibers from ventral row vibrissae terminate more dorsally. In like fashion, the rostral vibrissae terminate medially, whereas the caudal vibrissae terminate more laterally. Supraorbital vibrissae terminated within the ventral part of the nucleus, whereas mandibular vibrissae terminated more dorsally. The pattern was distributed so that each vibrissae was represented at practically all levels throughout V1. This pattern was at some variance with that described by Hayashi (1981, 1985a) who concluded that all low-threshold trigeminal afferents, including vibrissae, arborize in the lateral portion of V1. Physiologically identified and intraxonal stained vibrissae afferents terminating in V0 were morphologically indistinguishable from those terminating in V1 (Jacquin and Rhoades, 1990).

It is generally agreed that the shape of terminal arbors of vibrissae afferents and other types of low-threshold afferents that project to the MDH
FIGURE 5. The schematic diagram shown in the upper part of this figure illustrates the central distribution within the spinal trigeminal tract (T), and underlying subnuclei, of large-diameter low-threshold mechanoreceptive afferents (A-β) and small diameter high threshold afferents (htm). Note the shift in the central projection of pattern of the A-β fibers in the MDH. The tracings shown below the schematic diagram (a–i) show representative examples of terminal arbor morphology for different classes of afferents. The terminal arbors of primary afferent fibers innervating vibrissae are shown in a–c, guard hair follicles in d–f, and high-threshold mechanoreceptors in g–i. Roman numerals correspond to layers of MDH. Other abbreviations are same as in text. (Modified and adapted from Hayashi, H., J. Comp. Neurol. 237:195–215, 1985a, 240:71–89 (1985b). With permission.)

have a similar morphology in the rodent (Jacquin et al., 1984; Hayashi, 1985a). According to Jacquin et al. (1984), the collaterals of vibrissae primary afferents in MDH arborize in radial fashion and form a column that angles from layer V rostrally to layer III caudally. The topography of vibrissae afferents in the MDH generally follows the predictions of Dejerine (1914) who reported
the onionskin pattern of peripheral representation in the spinal trigeminal nucleus below the obex (i.e., more rostral vibrissae are represented rostrally and more caudal vibrissae are represented caudally). In cases of overlap (i.e., more than one vibrissae at the same rostrocaudal level), the mediolateral topography is reversed so that rostral vibrissae are lateral to the more caudal vibrissae. Jacquin et al. (1986) reported that vibrissae projections to the MDH were found in layer V, although the primary region of arborization was in layer III or IV. Hayashi did not observe terminal arbores from low-threshold afferents in layer V of the MDH, but he suggested that this might have been due to the relatively small number of vibrissae afferents that were included in the study.

B. Pulpal

1. Ganglion Cell Pulpal Afferents

The central distribution of nerves supplying the dental pulp has been the subject of many studies. Understanding the substrate for dental sensation is of obvious clinical interest. A troubling aspect of dental pain is the difficulty of the patient and sometimes the dentist to localize the source of stimulus. In addition to searching for a solution to the clinical problems of dental pain, basic research in dental sensory mechanisms presents a useful model system for the study of pain and nociception. A comprehensive review of this subject was presented by Dubner et al. (1978).

It is generally believed that pain is the only sensation to originate in the pulp. However, sensations referred to as dental “pre-pain” have been reported by several workers (see Dubner et al., 1978). Large-diameter myelinated fibers, which are typically associated with transmission of mechanoreceptive information, have been shown to enter the pulp chamber (Holland and Robinson, 1983). There is also physiological evidence that suggests that intradental receptors are capable of responding to mechanical transients (Dong et al., 1985).

Pulpectomy was shown to produce degeneration in brain-stem regions that convey or receive primary afferent input from the involved teeth (Westrum and Canfield, 1977). This phenomenon, termed transganglionic sensory degeneration (Grant and Arvidsson, 1975), made the silver degeneration techniques (Nauta-Gygax and Fink-Heimer) particularly useful for mapping the central projections of pulpal afferents (Anderson et al., 1977; Westrum and Canfield, 1977). The distribution of degenerating fibers and terminal boutons after pulpectomy was also studied at the ultrastructural level to determine details of synaptic connectivity (Gobel and Binck, 1977). Central degeneration resulting from pulpectomy is a matter for clinical concern, because these experiments imply that endodontic procedures prevent regeneration of nerve fibers that normally occur following injury in other tissues. It has been proposed that changes in the central synaptic circuitry resulting from permanent denervation may have important implications related to trigeminal pain mechanisms (Gobel and Binck, 1977). Questions related to developmental patterns, plasticity, and regeneration of these and other afferents (Jacquin et al., 1990) are exciting areas of ongoing research that merit a separate review.

According to Gobel and Binck (1977), unilateral mandibular pulpectomy results in degeneration of fibers that travel in the dorsomedial third of spinal trigeminal tract and terminate heavily in the periobex region. Using the terminology of Olszewski (1950), Gobel and Binck (1977) identified preterminal, terminal, and transynaptic degeneration in the marginal zone, substantia gelatinosa, and the magnocellular layer of Vc. This distribution included layer I, layer IIa, and layer V of MDH (Gobel, 1984). The dorsomedial location of degenerating fibers in MDH described by Gobel and Binck (1977) differed from other studies (Anderson et al., 1977; Westrum and Canfield, 1977; Johnson and Westrum, 1980), which found maxillary and mandibular dental representation to be restricted to the ventral half of V and MDH in periobex regions. However, there was general agreement that the primary projection was located in the ipsilateral periobex region, including parts of MDH and caudal V. The presence of contralateral degeneration, usually to a lesser extent than on the side of the pulpectomy, was also a consistent finding.

With the development of methods capable of demonstrating transganglionic transport of HRP (Mesulam, 1978), a number of studies were per-
formed to further examine the central projection of pulpal nerves in cats (Westrum et al., 1981; Arvidsson and Gobel, 1981; Shigenaga et al., 1986c) and rats (Marfurt and Turner, 1984). Many of these studies involved application or injection of HRP directly on the pulp. Arvidsson and Gobel (1981) compared the results of pulpal HRP injections with its application to the cut end of the inferior alveolar nerve. The transganglionic tracing methods revealed that the central distribution of pulpal afferents were much more extensive than originally thought and all subdivisions of spinal trigeminal nucleus were shown to contain labeled terminals (Westrum et al., 1981). Reaction product, indicating the distribution of pulpal afferents in the spinal tract and subjacent nucleus, was more dorsal in location than areas of terminal degeneration described in several of the earlier degeneration studies (Westrum and Canfield, 1977). Horseradish peroxidase-labeling studies led Westrum and Canfield (1977) to suggest that maxillary canine teeth were more strongly represented than mandibular canine teeth.

Two distinct pulpal projections were identified in cats by Arvidsson and Gobel (1981). The first was described as forming a long continuous column extending from the caudal part of the \( V_p \) through \( V_o \) and \( V_i \), into layer V of the MDH and upper cervical spinal cord. The second projection was restricted to layers I and IIa of MDH. The former projection was situated topographically within the medial part of the dorsal and middle thirds of \( V_p, V_o, \) and \( V_i \). The medial representation of dental afferents was in agreement with the general results of physiological studies. The laminar distribution of pulpal projections to MDH is consistent with the projection pattern of other nociceptive high-threshold afferents to similar cytoarchitectonic regions of spinal cord gray matter. These observations support the nociceptive function of pulpal afferents and of MDH.

In a study of the central distribution of neurons that innervate the rat maxillary molar teeth, Marfurt and Turner (1984) processed teeth that were injected with a mixture of native HRP and wheatgerm-agglutinated HRP. Processing the injection sites (molar teeth) provided a control to insure that the central projections identified in the study were due to uptake solely by pulpal nerves. This study revealed terminal labeling throughout the rostrocaudal axis of the trigeminal nuclei. Interestingly, the heaviest contribution from the rat molar teeth projected to the caudal half of \( V_p \) and rostral \( V_o \). Projections to the MDH were restricted to the dorsomedial portion of layers I, IIa, deep IV, and V, and these findings are generally consistent with the results of pulpal injections in cats. However, the distribution to \( V_i \) was somewhat heavier in rostral parts of this subnucleus, a finding that was not observed in cats (Arvidsson and Gobel, 1981; Westrum et al., 1981).

When ricin, a retrogradely and transneuronally transported neurotoxin, is injected into the pulp, it produces degeneration in both dorsal and ventral regions of the cat spinal trigeminal nucleus as determined by reduced-silver techniques (Johnson et al., 1987). There are several important considerations related to the use and interpretation of the silver-degeneration methods. It has been proposed that there are multiple manifestations of transganglionic sensory degeneration, some of which can only be determined by ultrastructural study. According to this theory, only the most severely affected fibers (i.e., those projecting to the ventral region of \( V_i \) and \( V_o \)) become argentophilic and are, therefore, demonstrable by reduced-silver techniques. The more extensive distribution of degenerating fibers observed after ricin administration results from the extensive damage to all afferents caused by this substance (Johnson et al., 1987). This type of selective response could account for apparent discrepancies between the central distribution of dental structures demonstrated with degeneration techniques when compared with axonal transport methods. Another critical factor is the selection of an appropriate survival time to optimally demonstrate degenerating fibers and terminals subsequent to the induction of lesions. These variables plus additional technical considerations related to the use of the axonally transported labels provide ample opportunity for differences in experimental outcome. Technical considerations aside, both physiological and anatomical studies show that tooth pulp afferents project to all parts of the spinal trigeminal nucleus. The pattern of distribution of single physiologically identified and intraaxonally pulpal afferents labeled is consistent with the pattern demonstrated with the
transganglionic methods (Shigenaga et al., 1986c). Single pulpal afferents have collaterals that project to the SVT_

\textsubscript{muy}, the caudal part of \textit{V}, and layers I and II of MDH (Shults, personal communication).

The presence of contralateral degeneration following unilateral pulpectomy remains somewhat enigmatic. One of the early controversies regarding pulpal innervation was related to the source of contralateral pulpal representation in the brain stem. Horseradish peroxidase injections into the pulp were reported to result in bilateral labeling of cells in the trigeminal ganglion (Anderson et al., 1977). This was interpreted as evidence for transmedian innervation of teeth that extended as far as the contralateral canine teeth. The bilateral innervation to the canine teeth would also explain the source of bilateral degeneration following unilateral pulpectomy or tooth extraction (Westrum and Canfield, 1977). This theory seemed particularly attractive, but lost some support from early transganglionic transport studies of pulpal projections that failed to demonstrate labeled fibers or terminal labeling in the contralateral trigeminal nuclei (Westrum et al., 1981; Arvidsson and Gobel, 1981). There was some physiological evidence in support of transmedian innervation (reviewed in Anderson et al., 1977). Certain conditions would seem to favor development of at least some transmedian innervation. It has been shown that sectioning the inferior alveolar nerve induces collateral sprouting from the lingual and mylohyoid nerves (Robinson, 1981). There is no \textit{a priori} reason to assume that some fibers might not originate as collaterals from the contralateral inferior alveolar nerve, but the reinnervation study of Robinson (1981) indicated that the contralateral inferior alveolar nerve was not a source of the collateral reinnervation. In addition, the existence of significant transmedian innervation has not been confirmed in a number of related degeneration and axonal transport studies (Fuller et al., 1979; Arvidsson and Gobel, 1981; Marfurt and Turner, 1984).

Recent studies have shown that trigeminal primary afferent fibers do project to the opposite spinal trigeminal nucleus in rodents (Jacquin et al., 1982, 1990; Jacquin and Rhoades, 1990; Marfurt and Rajchert, 1991; Westrum and Henry, 1991). However, it is unlikely that these decussating fibers are pulpal in origin. The results of a series of transport experiments in normal rats and in rats that had been subjected to infraorbital nerve section at birth (Jacquin et al., 1990) provided data that nociceptive fibers are not a component of the centrally decussating primary afferent projections. A more recent publication (Panneton et al., 1991) suggests that this innervation is related primarily to low-threshold mechanoreceptors located in midline hairy skin rather than small-diameter fibers that comprise the majority of pulpal innervation. It seems, therefore, that the issue of contralateral degeneration following pulp extirpation has not been resolved entirely, although theories such as distal transsynaptic degeneration (Westrum and Henry, 1991), degeneration as a result of natural exfoliation, or continual loss of pulp innervation throughout life, coincident with reduction in the size of the pulp chamber, may all contribute to contralateral degeneration observed following unilateral pulpal lesions.

2. Pulpal Afferents in the Mesencephalic Trigeminal Nucleus

An autoradiographic study (Chiego et al., 1980) reports the existence of a few labeled cells in \textit{V}_{mes} following treatment of the pulp with tritiated amino acids. The presence of a \textit{V}_{mes} contribution to the pulp in adult animals remains somewhat controversial because they were not observed in several tracer studies (Capra et al., 1984; Marfurt and Turner, 1984). However, recent evidence shows that treatment of the pulp with antiinflammatory agents results in the labeling of \textit{V}_{mes} neurons following HRP application (Yoshino et al., 1989). The authors reasoned that this treatment prevented inhibition of axonal uptake and transport caused by edema as a result of trauma. Most recently, Henry and Westrum (1990) demonstrated labeling in \textit{V}_{mes} and in other nuclei in the trigeminal system, subsequent to pulp injections. This study was performed in kit-

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sentation of deciduous teeth. This is an important experiment because it recognizes and attempts to evaluate the topographical reorganization that might occur during the development of permanent dentition. Studies of this type raise important issues regarding which morphological questions are of biological significance when interpreting the functional patterns of trigeminal representation in the central nervous system. Although attempts have been made to sort out distinctions between the central vs. peripheral distribution of pulp and periodontal ganglion cell afferents (Capra et al., 1984), the more important question may be less demanding of our technical energies. Rather than pursue the issue of whether a few fibers from the Vmes may stray into the pulp chamber, it may be more meaningful from clinical and basic perspectives to evaluate the central trigeminal representation of individual teeth, and their supporting structures, by considering the pulp and periodontium as elements of a complex sensory organ ideally suited for mastication. This concept may be strengthened further as our knowledge increases regarding the functional properties of Vmes and ganglion cell projections from dental structures (i.e., pulp-periodontal complex) onto cells in Vp, Vo, and other brainstem nuclei.

C. Periodontal

The periodontal ligament surrounding the teeth is known to contain a variety of neuronal sensory endings (Berkovitz et al., 1983; Bernick, 1957; Bonnau et al., 1978; Brashear, 1936; Byers, 1984, 1985, 1986; Byers and Dong, 1989; Byers and Holland, 1977; Corpron et al., 1980; Frank et al., 1976; Harris, 1975; Kizior et al., 1968; Lewinsky and Stewart, 1925; Millar et al., 1989). The most intensely studied of these afferents, both physiologically and anatomically, are the low-threshold mechanoreceptor afferents that respond to tooth displacement (for review see Anderson et al., 1970; Hannam, 1976, 1982; Steenberghge, 1979). Higher-threshold afferents are also known to exist in the periodontal ligament (Mei et al., 1975); however, the specific central distribution of these afferents has not been determined.

The cell bodies of periodontal mechanoreceptor afferents are located in both the gasserian ganglion (Appenteng et al., 1982b; Beaudreau and Jerge, 1968; Mei et al., 1975) and Vmes (Appenteng et al., 1978; Jerge, 1963a; Linden, 1978). The majority of these cells have a pseudo-unipolar morphology. A small number of multipolar cells in Vmes, however, have been retrogradely labeled from the alveolar nerves (Gottlieb et al., 1984; Nomura and Mizuno, 1985; Nomura et al., 1985) and Shigenaga et al. (1988b) reported one bipolar periodontal cell.

The central distribution of these afferents has been examined indirectly (a) via fiber staining and degeneration (Gonzálo-Sanz and Insausti, 1980), (b) by the application of neuronal tracers onto the alveolar nerves (Nomura and Mizuno, 1985; Nomura et al., 1985; Jacquin et al., 1983; Segade et al., 1990; Takemura et al., 1987), and more directly (c) via the application of tracers on the periodontal ligament (Capra and Wax, 1989; Gottlieb et al., 1984), and (d) with intracellular staining techniques (Shigenaga et al., 1988, 1989; Tsuru et al., 1989).

1. Periodontal Mechanoreceptors Located in Vmes

Periodontal afferents with their cell bodies located in Vmes tend to be concentrated in the caudal portion of the nucleus (Capra and Wax, 1989; Gottlieb et al., 1984; Linden, 1978; Nomura and Mizuno, 1985) with axons that exit the brain stem either in the motor root of V or the sensory root of V (Shigenaga et al., 1989). Retrograde labeling from injections surrounding the teeth indicate that Vmes periodontal cells participate in the small clusters that occur within this nucleus (Gottlieb et al., 1984), although the precise arrangement of afferent modalities comprising these clusters has not been determined. Synaptic contacts have been reported onto Vmes periodontal afferents (Inagaki et al., 1987), although the nature of this synaptic input is not known.

The mesencephalic nucleus of the trigeminal nerve contains both rapidly and slowly adapting periodontal afferent neurons (Amano and Iwasaki, 1982; Beaudreau and Jerge, 1968; Hannam,
Periodontal and trigeminal afferent distribution in the brain stem has been studied extensively, with a focus on the periodontal nerve (Jacquin et al., 1983). No evidence of a projection from \( V_{\text{mes}} \) to the cerebellum has been found in intra-axonal staining studies in spite of the close proximity of the injection sites to the superior cerebellar peduncle (Shigenaga et al., 1988b, 1989).

### 2. Periodontal Mechanoreceptors Located in the Trigeminal Ganglion

Periodontal ganglion cell afferents tend to be located in the posterolateral portion of the mandibular and maxillary divisions of the trigeminal ganglion (Capra and Wax, 1989; Gregg and Dixon, 1973; Marfurt, 1981). The axons of these afferents course centrally and either bifurcate into an ascending and descending process or they descend directly in the tract of the spinal trigeminal nucleus without bifurcation (Tsuru et al., 1989). Tsuru et al. (1989) found that the ratio of descending nonbifurcating to bifurcating fibers was about the same for primary afferents located in the periodontal ligament and the tooth pulp. These authors interpreted this to mean that both bifurcating and descending nonbifurcating fibers play an important role in mediating tactile and nociceptive information.

Rapidly adapting mechanoreceptors were associated with afferents that bifurcated at the rostral level of \( V_o \) and those that did not bifurcate. Collaterals from both types coursed into \( V_{\text{pc}} \) and \( V_o \). The slowly adapting periodontal mechanoreceptors also were associated with afferents that bifurcated and some that descended directly in the spinal tract of the trigeminal nerve. Collaterals from the slowly adapting afferents also projected to \( V_p \) and \( V_o \).

Studies that report the central distribution of afferents located within the alveolar nerves differ from the intra-axonal staining studies in several aspects. These studies show terminal labeling in the entire spinal trigeminal nucleus, the supra- and mesencephalic regions, the cerebellar nuclei, and the solitary tract, PCRF, as well as the upper cervical spinal cord and the cerebellum (Jacquin et al., 1983; Nomura and Mizuno, 1985; Shigenaga et al., 1989; Takemura et al., 1987). Whether this labeling results from the distribution of nonperiodontal mechanoreceptor afferents or whether
these techniques are more sensitive in indicating the caudal extent of periodontal afferents remains to be determined.

D. Oral Mucosa, Palate, and Tongue

The projection of intraoral afferents other than pulpal and periodontal has been demonstrated in cats by studying the pattern of transganglionic transport of HRP that was applied to the cut end of nerves supplying intraoral tissues (Shigenaga et al., 1986a, b) or injected directly into specific intraoral regions (e.g., palate; Arvidsson and Hellstrand, 1988). Similar experiments have been conducted in rats (Liem et al., 1990). All major trigeminal sensory nuclei receive intraoral input. Intraoral structures were shown to have an exclusive, but complex representation in the feline Vp. Lingual nerve fibers projected solely to Vpd. Labeling from all the nerves innervating intraoral structures was distributed mainly in the dorso-medial regions of Vo and Vi (Shigenaga et al., 1986b). Intraoral primary afferents were distributed within the trigeminal sensory nuclei so that the pattern of an inverted face with the mouth open medially could be identified. This pattern extended from rostrocaudal levels of Vp, through the caudal levels of Vi, forming a rostrocaudally oriented column with some variation in density of reaction product. Caudally projecting fibers from intraoral structures in cats terminated in the dorsomedial and intermediate region of MDH. Lingual nerve representation was heaviest in layers I to III of the rostral MDH, the inferior alveolar nerve was represented throughout layers I to V of all levels of MDH, and representation of the buccal nerve was limited to the caudal two thirds of MDH. Intraoral maxillary representation was limited to the rostral one third of MDH, terminating primarily in layers I, II, and V. Tongue and palatal afferents were distributed in a rostrocaudal fashion, suggesting that representation of these structures in MDH is rotated 90° to that of the facial surfaces (Shigenaga et al., 1986a).

Horseradish peroxidase injections made into the incisive papilla produced bilateral terminal labeling in the rostralmost part of Vpd with a small projection to the Vp, that continued throughout Vo, Vi, the nucleus of the solitary tract, and the lamina I/II border of MDH. Scattered label was observed in the interstitial nuclei from the level of Vo extending caudally into the transition (alaminar) zone between Vi and MDH. Injections made in the region of the palatine foramen resulted in ipsilateral labeling of a lesser intensity than that seen following injections of the incisive papilla. The terminal labeling resulting from injections into the palatine foramen was slightly more dorsal and caudal to that observed following injections around the incisive foramen (Arvidsson and Hellstrand, 1988). This distribution was similar to that proposed by Shigenaga (1986a).

E. Muscle

1. Neuromuscular Spindle

a. Cell Morphology and Distribution within the Mesencephalic Trigeminal Nucleus

It has been known for more than 50 years that some Vmes cells project peripherally to muscle spindles within the muscles of mastication (Szentagothai, 1948). A limited topographic organization of spindle afferents exists in Vmes. Masseter, temporals, and medial pterygoid muscle afferents are distributed along the entire length of the nucleus (Arvidsson and Raappana, 1989; Capra et al., 1985; Gottlieb et al., 1984; Nomura and Mizuno, 1985; Rokx et al., 1985, 1986), whereas muscle afferents from the lateral pterygoid muscle and periodontal afferents are concentrated more caudally (Capra and Wax, 1989; Gottlieb et al., 1984; Nozaki et al., 1985).

b. Central Projections of Jaw-Muscle Spindle Afferents

Intracellular staining of Vmes cells and axons has provided the most specific information about the anatomical projections of trigeminal muscle spindle afferents (Appenteng et al., 1985; Dessem and Taylor, 1989a; Lingenhöhl and Frauf, 1991; Shigenaga et al., 1988a, 1990a). In all of these studies the axons of jaw-muscle spindles are reported to enter the brain stem in the motor root of the trigeminal nerve and course dorso-
medially toward V_{mot}. The majority of the axons penetrate V_{mot} and then bifurcate either within the motor nucleus or dorsolateral to it into rostrally and caudally projecting processes (Figure 6). The rostral projection of these axons course in the tract of the mesencephalic nucleus. Caudally, they form a descending fiber bundle, originally described by Probst (1899) and that is now commonly designated as the tract of Probst (Corbin, 1942). In cats, a subset of these V_{mes} were identified and designated as the delayed mesencephalic fibers by Thelander (1924), using the Marchi method. This bundle consists of a small number of fibers that pass more caudal and ventral than the majority of V_{mes} fibers. Evidence for this variation has also been described in the rat (Dessem and Taylor, 1989a), although the functional significance of this separation remains unknown.

c. Projection to the Trigeminal Motor Nucleus

Intracellular staining studies have found a consistent V_{mes} projection to V_{mot}. In the cat, Shigenaga et al. (1988a, 1990a) describe distinctly different distributions to V_{mot} for spindle afferents that they classified as type I and type II. These authors report that type I afferents have terminal arbors throughout the entire rostrocaudal extent of V_{mot}. In the rostral two thirds, terminal arbors encompass all of the motor nucleus, whereas caudally, they occupy only its dorsal and lateral regions. In contrast to this, the type II afferents of Shigenaga et al. (1988a, 1990a) have terminal arbors distributed to the dorsal or lateral borders of V_{mot}, and the boutons of type II are always restricted to two or three small areas near the lateral boundaries of the motor nucleus.

FIGURE 6. This shows the central distribution of a single filled masseter muscle spindle afferent. This is a sagittal reconstruction extending over 1200 μm. This is an example of the type of detailed architecture that can be obtained by intracellular and intraxonal filling of physiologically identified neurons with markers such as horseradish peroxidase. The dotted line represents the ventral border of the brain stem, the dashed line outlines the trigeminal motor nucleus. (From Dessem and Taylor, J. Comp. Neurol., 282:389–403 (1989) With permission.)
Intracellular staining studies in the rat (Appenteng et al., 1985; Dessem and Taylor, 1989a; Lingenhöhöl and Friauq, 1991; Luo et al., 1991) have described axon collaterals of muscle spindle afferents that have projections restricted to a small region of $V_{mot}$. Luo et al. (1991) described masseteric $V_{mot}$ afferents, terminating in the dorsolateral division of the motor nucleus, confined to the nuclear borders, and extending only slightly to the central area of the nucleus. The restriction of boutons to the borders of $V_{mot}$ may also be seen in Figure 7 (Dessem and Taylor, 1989a). These data suggest that all jaw-muscle spindle afferents in the rat have a restricted distribution similar to that described by Shigenaga et al. (1988a, 1990b) for their type II afferents.

Further support for a synaptic connection from jaw-muscle spindle afferents to trigeminal motoneurons is provided by electrophysiological studies using spike-triggered averaging (Appenteng et al., 1978; Appenteng et al., 1989; Nozaki et al., 1985). These studies use the action potentials of identified jaw-muscle spindle afferents located in $V_{mot}$ as a trigger to generate an average of either trigeminal motoneuron membrane potentials or extracellular field potentials that are correlated with the spindle activity. Appenteng et al. (1978) and Nozaki et al. (1985) have demonstrated that short-latency depolarizations of the membrane potential recorded intracellularly from trigeminal motoneurons correlated with the firing of single jaw-muscle spindle afferents. These authors characterized these depolarizations as unitary excitatory postsynaptic potentials (EPSPs) that ranged in amplitude from 3.1 to 60 $\mu$V.

Eighty-five percent of the trigeminal motoneurons examined by Appenteng et al. (1978) and 66% of those examined by Nozaki et al. (1985) showed no evidence of unitary EPSPs, leaving these authors to conclude that the projection of jaw-muscle spindle afferents to trigeminal motoneurons was much more restricted than in the spinal cord where motoneurons receive monosynaptic input from nearly every spindle (Mendell and Henneman, 1971).

The location of jaw-muscle spindle afferents boutons on trigeminal motoneurons have been estimated using the EPSP shape criterion of Rall (1967). Unitary monosynaptic EPSPs from temporalis, masseter, and medial pterygoid muscle spindle afferents suggest that these contacts are mostly located on the distal dendrites of trigeminal motoneurons, whereas those from the lateral pterygoid muscle are located on the more proximal portions of the dendrites (Appenteng et al., 1978; Chandler et al., 1980; Nozaki et al., 1985).

d. Projections Dorsal to the Trigeminal Motor Nucleus

Axon collaterals and boutons of jaw-muscle spindle afferents have been observed consistently in the region dorsal to $V_{mot}$ (Appenteng et al., 1985)
1985; Dessem and Taylor, 1989a; Shigenaga et al., 1988a, 1990a). In the rat, Dessem and Taylor (1989a) found collaterals from all stained jaw-muscle spindle afferents in this region and the largest number of boutons in this region. In this study, it was not possible to determine how many of these boutons contacted cells intrinsic to this region and how many may have been in contact with trigeminal motoneurons that send their dendrites into this region (Mong et al., 1988; personal observation, D.D.). Recently, Luo et al. (1991) has demonstrated the close apposition between intracellularly stained cells and stained boutons of masseter Vmes afferents that presumably represent synaptic contacts between muscle spindles and cells of the supratrigeminal region.

In the cat, Shigenaga et al. (1988a, 1990b) report that the two types of jaw-muscle spindle afferents that they identified have different projections to the supratrigeminal region. Type I projects predominantly to Vmot and has only a very sparse projection to the surrounding region. In contrast, the type II afferents have an extensive projection to the region dorsal to Vmot.

Further support for a projection of jaw-muscle spindle afferents to this region comes from electrophysiological studies in cats and rats (Appenteng et al., 1989; Jerge, 1963b; Miyazaki and Luschei, 1987; Takata and Kawamura, 1970; Gura et al., 1972). Unitary extracellular recordings in this region are modulated during jaw-muscle stretch (Jerge, 1963; Miyazaki and Luschei, 1987) and intracellular recordings (Takata and Kawamura, 1970) appear to confirm the existence of cells in this region receiving muscle spindle input.

e. Projections to the Intertrigeminal Region

In the rat, Luo et al. (1991) describe boutons from Vmes muscle afferents in the Vint. Dessem and Taylor (1989a), however, did not find boutons from jaw-muscle spindle afferents located far enough ventrally to be considered in Vint as defined by Lorente de Nó (1922). In the cat, Shigenaga et al. (1988a, 1990a) describe projections from jaw-muscle spindle afferents to a region they designate as the intertrigeminal region, which appears to be an area located more dorsally than Vint described by Lorente de Nó.

f. Mesencephalic Trigeminal Nucleus, Intranuclear Projections

Projections from rostrally located Vmes cells onto cells in the caudal portion of the nucleus were originally described by Rámon y Cajal (1909) using Golgi techniques. Recent intracellular staining studies have confirmed the existence of these projections in rats (Dessem and Taylor, 1989a) and cats (Shigenaga et al., 1990a) and demonstrated that some of these intranuclear projections are from rostrally located jaw-muscle spindle afferent cells. No evidence is available as to whether these contacts are onto other jaw-muscle spindle cells or onto periodontal afferents.

g. Projections Caudal to the Trigeminal Motor Nucleus

All well-stained jaw-muscle spindle afferents that have been described send a caudal projection into the tract of Probst (Appenteng et al., 1985; Dessem and Taylor, 1989a; Shigenaga et al., 1988a, 1990a). As this process descends in the brain-stem, axon collaterals are given off into various brain stem regions. Axon collaterals have been observed consistently in the reticular formation, and some of these collaterals extend far enough lateral to reach the trigeminal sensory complex (Appenteng et al., 1985; Shigenaga et al., 1990a).

In the rat, Dessem and Taylor (1989a) found collaterals that coursed into the reticular formation immediately caudal to the Vmot. It was not possible to determine whether these collaterals contacted cells in this region or the distal dendrites of trigeminal motoneurons. Physiological evidence indicates that some cells in this region are responsive to jaw-muscle stretching (Appenteng et al., 1989). Cells in this region also project to the ipsilateral Vmes (Appenteng and Saha, 1988) and could provide an indirect pathway for muscle spindle afferent input to reach the motor nucleus. Additional axon collaterals project from the tract of Probst into the reticular formation medial to
the spinal trigeminal nucleus at the level of the facial motor nucleus and terminate. This region appears to correspond to the nucleus of Probst designated by Matesz (1981). Cells in this region have been shown to project to the trigeminal motor nuclei (Mizuno et al., 1983; Travers and Norgren, 1983; Vornov and Sutin, 1983; Appenteng and Girdlestone, 1987). Cells in the dorsal part of the reticular formation, at this level, are presumed to be the origin of preganglionic parasympathetic fibers innervating the salivary glands (Nicholson and Severin, 1981).

In the cat, Shigenaga et al. (1988a, 1990a) described axon collaterals and boutons in a region they designate as the juxtatrigeminal region. This region appears to correspond to the PCRF, including the nucleus of Probst described by Matesz (1981). Shigenaga et al. (1990a) have also described axon collaterals and boutons projecting to the dorsomedial and rostromedial portions of the V₃.

h. Morphology of Classified Jaw-Muscle Spindle Afferents

Several criteria have been used to identify jaw-muscle spindle afferent responses prior to intracellular staining. Some studies have used the response of the afferents to propping or stretching of the jaw muscles (Appenteng et al., 1985; Dessem and Taylor, 1989b; Shigenaga et al., 1990a). Although this scheme may be sufficient to identify sensory afferents as originating in muscle spindles, it is not sufficient to differentiate primary, secondary, or intermediate muscle spindle afferents. In the spinal cord, muscle spindle primary and secondary afferents can be differentiated on the basis of their conduction velocity (Hunt, 1954). In the trigeminal system, there is no clear separation between the fiber diameters of primary and secondary muscle spindle afferents (Morimoto et al., 1982). This feature, combined with the short conduction distances of the cranial nerves, does not allow jaw-muscle spindle primaries and secondaries to be separated on the basis of conduction velocity (Inoue et al., 1981). An additional consideration is that physiological and anatomical studies indicate the presence of tandem and intermediate afferents in the jaw-muscle spindles (Banks et al., 1988; Dessem and Taylor, 1989b; Karlsen, 1965; Taylor and Durbaba, 1990). The functional implications of these morphological variations have not been resolved.

Shigenaga et al. (1990a) classified intracellularly labeled jaw-muscle spindles into two morphologically distinct groups and found no significant differences in the response patterns of these afferents to sustained jaw opening. These authors then suggested that primary and secondary jaw-muscle spindle afferents have distinctive morphologies but cannot be distinguished on the basis of their response patterns. This conclusion is premature for several reasons. Shigenaga et al. (1990a) were not able to correlate their two types of axonal trajectories with the morphology of the afferent endings in the muscle spindle and, therefore, based their identification on the response properties of the afferents. Muscle spindle afferents, however, are usually classified on the basis of their response during the dynamic phase of muscle stretch and not the response generated during a brief period of sustained muscle stretch as used by Shigenaga et al. (1990a). To differentiate muscle spindle afferent responses during sustained muscle stretch requires a comparison of the coefficient of variation of thousands of interspike intervals (Matthews and Stein, 1969; Stein and Matthews, 1965). These authors also give no indication of the amplitude and velocity used to stretch the jaw muscles and, therefore, it is not possible to compare their responses with the responses of classic primary and secondary afferents (Matthews, 1972). Finally, there is increasing evidence that muscle spindle afferent responses need to be classified on the basis of their responses following the infusion of depolarizing drugs so that the relationship of sensory endings to bag and chain fibers can be distinguished (Cody et al., 1972; Dutia, 1980; Durbaba et al., 1991; Price and Dutia, 1987; Taylor and Durbaba, 1990). Further studies are needed, therefore, to determine the central distribution of rigorously differentiated jaw-muscle spindle primary, secondary, intermediate, and tandem afferents.
i. Mesencephalic Trigeminal Central Projections, General

Additional information on the anatomical distribution of \( V_{\text{mes}} \) afferents can be obtained from experiments that involve injecting the nucleus or its central targets and tracing anterogradely or retrogradely transported label (Luschei, 1987; Matesz, 1981; Mizuno and Sauerland, 1970; Rokx et al., 1986; Ruggiero et al., 1982; Stainer and Gilbert, 1989). Although these studies do not provide information about the projection of specific afferent modalities, they are useful because they sample a much larger number of \( V_{\text{mes}} \) afferents than is currently available from intracellular staining studies. Specific antibodies to label \( V_{\text{mes}} \) projections (Poltorak and Freed, 1987) support the projection of \( V_{\text{mes}} \) to \( V_{\text{mot}} \), the supratrigeminal region, the nucleus of Probst, the parvocellular reticular formation, and portions of the spinal trigeminal nucleus, as reported in the intracellular staining studies. Some of these studies (Matesz, 1981; Stainer and Gilbert, 1989) also report \( V_{\text{mes}} \) projections to the cerebellum and cervical spinal cord that is consistent with experiments in which branches of the trigeminal nerve have been exposed to neuronal tracers. Sparse projections to the facial motor nucleus, the hypoglossal motor nucleus, and the solitary nucleus have also been identified in these experiments.

j. Neurotransmitters

Only limited information is available on the neurotransmitters released by the terminals of jaw-muscle spindle afferents. Chandler (1989) has shown that field potentials recorded in \( V_{\text{mot}} \) elicited by stimulation in the \( V_{\text{mes}} \) are reduced when excitatory amino acid antagonists are iontophoresed into \( V_{\text{mot}} \). These data suggest that excitatory amino acids are involved in the pathway from jaw-muscle spindles to \( V_{\text{mot}} \). This finding is particularly interesting because the membrane conductance recorded in the cell bodies of \( V_{\text{mes}} \) cells is not affected by glutamate (Henderson et al., 1982). Although a number of other studies have shown that trigeminal motoneuron activity evoked by stimulation in the region of \( V_{\text{mes}} \) can be modified by the systemic infusion of drugs, it is likely that these are postsynaptic effects (Iwata et al., 1971; Morilak and Jacobs, 1985; Soja et al., 1987).

k. Jaw-Muscle Afferent Projections Based on Whole Nerve Studies

Several studies have investigated the central distribution of jaw-muscle afferents by injecting anatomical tracers into the muscle or applying them to the muscle nerves (Capra and Wax, 1989; Nomura and Mizuno, 1985; Shigenaga et al., 1988). These studies have not only reported \( V_{\text{mes}} \) projections to the regions described by intracellular methods (i.e., \( V_{\text{mot}}, V_{\text{sup}}, V_{\text{int}}, \) reticular formation, parts of the spinal trigeminal nucleus) but have also reported labeling in more caudal regions of the brain stem (i.e., spinal cord, ventral border of the solitary nucleus, lateral border of the hypoglossal nucleus, cerebellum). These differences probably result from the labeling of nonspindle muscle afferents located in the trigeminal ganglion and perhaps in \( V_{\text{mes}} \). Other differences may also be due, in part, to incomplete filling of \( V_{\text{mes}} \) axons in the intracellular studies. Alternatively, it may be that only a small number of \( V_{\text{mes}} \) cells project to some of these regions and they have not been sampled in sufficient numbers with intracellular labeling methods. Of particular interest is the lack of a projection to the cerebellum, even though the injection sites were quite close to the superior cerebellar peduncle.

2. Tendon Organ and Other Muscle Receptors

In addition to muscle spindles, Golgi tendon organs, lamellated (encapsulated) receptors, and unmyelinated nerve endings have been reported in the muscles of mastication (Franks, 1964; Kawamura and Hamada, 1974; Sakada et al., 1974; Lund et al., 1978). However, there is very little evidence regarding the morphology of these receptors. Several structures similar to the dyads...
that consist of a spindle and a tendon organ, as reported in the cat by Lund et al. (1978), have been identified in masticatory muscle tissue prepared for high-resolution microscopy. Although these structures were similar in appearance to the ends of the tendon organs reported by Marchand et al. (1971), distinctive sensory regions demonstrating large collagenous bundles with a specific association to finely branched terminal processes of nerve fibers, similar to those demonstrated in the human lumbrical muscles (Nitatori, 1988), were never observed in jaw muscles. Examination of serial sections through these structures invariably revealed that the smaller unit of the dyad was actually the neurovascular bundle that supplies the equatorial and/or polar regions of the adjacent spindle (Figure 8 unpublished observations, NFC). These encapsulated bundles contain a relatively large number of collagen fibers, the expected complement of myelinated axons, and at least one bundle of unmyelinated axons. Physiological data obtained from studies of Vmes neurons that can be attributed to tendon organs is tentative at best (Dubner et al., 1978). It is also probable that nonspindle muscle receptors would be innervated by trigeminal ganglion. This issue clearly deserves further analysis.

Single-unit recording studies show that high-threshold muscle afferents project to both Vc and Vl. Many of the cells in Vl that Hayashi et al. (1984) characterized as low-threshold mechanoreceptors (LTM), wide-dynamic range (WDR), or nociceptive specific (NS) afferents could also be excited by high-strength stimulation of the masseter nerve. Amano et al. (1986) described neurons in Vc that were responsive to the injection of algesic chemicals into the blood supply of the muscles of mastication (Amano et al., 1986), and Kojima (1990) found afferents activated by noxious mechanical and thermal stimulation of the masseter muscle.

Trigeminal ganglion cells supplying the muscles of mastication, for the most part, have small cell bodies (Capra and Wax, 1989; Nishimori et al., 1986; Shigenaga et al., 1988a). Presumably, the small cells give rise to small myelinated and unmyelinated fibers. Observations regarding size of labeled somata has been cited in support of the view that these fibers are primarily responsible for conducting information related to muscle nociception (Nishimori et al., 1986; Shigenaga et al., 1988).

Transganglionic and double-labeling studies of the central projection of trigeminal ganglionic muscle afferents reveal a substantial projection to Vl and Vc and the adjacent PCRF (Arvidsson and Raapana, 1989; Capra and Wax, 1989; Nishimori et al., 1986; Shigenaga et al., 1988a). Physiological evidence supports the convergence of trigeminal muscle afferents and neck muscle afferents onto cells in the upper cervical spinal cord (Abrahams et al., 1979). Projections to rostral portions of the spinal trigeminal nucleus, the cervical spinal cord, the contralateral Vl and cervical spinal cord, SVTins, the vestibular nucleus, the nucleus of the solitary tract, the reticular formation, the cuneate nucleus, the hypoglossal nucleus, and the cerebellum have also been reported (Pfaller and Arvidsson, 1988; Marfurt and Rajchert, 1991; Segade et al., 1990). Determination of whether most of these projections involve transmission of high- or low-threshold information awaits further study.

F. Joint

1. Temporomandibular Joint

Joint receptors were traditionally thought to serve the primary task of providing the central nervous system with sensations related to position or kinesthetic sense. The temporomandibular joint (TMJ) contains numerous unmyelinated nerve endings (Sessle and Hu, 1991), Ruffini-like endings, and two types of encapsulated receptor (Dubner et al., 1978; Thilander, 1961). Because Vmes was known to be primarily involved in providing proprioceptive information to the central nervous system (Szentágothai, 1948), early neuroanatomists suggested that the TMJ might be innervated by cells in Vmes (Crosby et al., 1964). Romfh et al. (1979) injected the TMJ with HRP and demonstrated that the neurons innervating the joint were located in the mandibular region of the trigeminal ganglion and not in Vmes.
FIGURE 8. The four light photomicrographs on the left side were selected from a serially sectioned spindle to illustrate the relationships between the neuromuscular spindle and the adjacent neurovascular bundle. (A) This is the juxtaequatorial region of the spindle on the right. The neurovascular bundle on the left contains a modest number of nerve fibers, varying in diameter. Note the change in orientation of the largest of these fibers (arrowhead). (B) As sections progress toward the equator, the largest myelinated fibers (arrowheads) turn away from the bundle to enter the spindle capsule. (C) This section is taken from the spindle equator. The large myelinated fibers are in the spindle capsule (lower arrowhead), whereas smaller fibers are just penetrating the capsule (upper arrowhead). Note the diminution of nerve fibers adjacent to the spindle. (D) This section was taken just beyond the equator. Note the relatively small size of the neurovascular bundle (arrowhead). The photomontage of electronmicrographs on the right illustrates the morphology of a typical neurovascular bundle located adjacent to a spindle in the same approximate relationship as the light micrographs on the left. The neurovascular bundle is outlined. Note the presence of unmyelinated nerve fibers (umnf) and the Schwann cell (sc) nucleus of a small myelinated fiber. These bundles contained a rather large amount of collagen (arrowheads) that continued into the capsule. The neurovascular bundle and the spindle appear to share the same connective tissue capsule (SpC), and fibroblasts (Fb) are numerous inside and outside of the spindle. Typically, these structures were associated with relatively large blood vessels (V), which also shared the spindle capsule.
These observations were supported by extracellular recording from ganglion cells in rabbits (Appenteng et al., 1982b). The study by Lund and Matthews (1981) and Appenteng et al. (1982b) provided evidence that some of the ganglion cell joint afferents were capable of signalling relatively precise changes in jaw position. As with joint receptors in other parts of the body, some of these receptors responded to limits of motion and most of them showed a hysteresis in the firing frequency as the joint returned to rest position.

Transganglionic transport of HRP has been used to trace the central projections of joint afferents in the brain stem (Capra, 1987). Reaction product, indicative of terminal labeling, was distributed throughout the dorsal part of the V₃, pars γ of V₂, V₃, and the dorsomedial region of MDH. Labeling in MDH was found in layers I, II, and III.

It is likely that the unmyelinated endings in the TMJ are associated with small-diameter fibers that project to MDH and signal noxious stimuli originating in the joint (Sessle and Hu, 1991). Extracellular microelectrode studies have verified TMJ representation in the MDH (Broton et al., 1988). Cells in this region that receive input from the joint also receive input from facial and introral structures. Although some of these cells received input exclusively from LTM, most were NS or WDR neurons that responded to noxious and nonnoxious stimuli. These data strongly support the concept that joint input to the MDH is involved in nociceptive mechanisms and that the NS and WDR neurons show a particular sensitivity to high-intensity electrical stimulation, algesic chemical stimulation, and intense mechanical stimulation of the surrounding articular tissues (Sessle and Hu, 1991). It is of some interest that many of the physiologically identified cells were localized to deeper layers of the MDH rather than in layers I to III.

2. Sutural/Symphysis

The mandibular symphysis is the midline joint between the two hemimandibles that remains unfused in many mammals (Beecher, 1979; Scapino, 1965, 1981). This region receives innervation from mandibular branches of the trigeminal nerve and contains a variety of nerve endings (Scapino, 1965). Physiological recordings from the gasserian ganglion in rabbits (Appenteng et al., 1982b) indicates that slowly adapting afferents located in the mandibular symphysis are activated during jaw movements. The central distribution of these afferents is not known.

G. Periosteal

Free nerve endings, complex unencapsulated nerve endings, and encapsulated nerve endings are located in the periosteum of the mandible and skull (Sakada and Aida, 1971a,b; Sakada and Maeda, 1967; Sakada and Taguchi, 1971). These receptors are thought to convey vibratory, pressure, thermal, and noxious modalities based on the diameter of their afferent axons and physiological characteristics (Sakada, 1983; Sakada and Maeda, 1967; Sakada and Miyake, 1972; Sakada and Nemoto, 1972; Sakada and Yano, 1978). Their cell bodies are located in the trigeminal ganglion (Hill and Elde, 1988), but the central distribution of these afferents is not known.

H. Meningeal and Cerebrovascular

Trigeminal afferents whose cell bodies are located in the trigeminal ganglion innervate the meninges and cerebral vasculature (Arbab et al., 1986; Borges and Moskowitz, 1983; Keller et al., 1985; Liu-Chen et al., 1984; Mayberg et al., 1981; McMahon et al., 1985; O'Connor and Kooy, 1986; Steiger et al., 1982; Suzuki et al., 1989; Uddman et al., 1989). Recent electrophysiological studies have shown that electrical stimulation of the dura and meningeal arteries can activate cells in all three divisions of the spinal trigeminal nucleus (Davis and Dostrovsky, 1986, 1988a,b; Strassman et al., 1986). Most of the sensory fibers innervating the pial and dural vessels of the anterior cranial fossa have cell bodies situated in the ophthalmic division of the trigeminal ganglion (O'Connor and Kooy, 1986),
but posterior fossa vessels are innervated by upper cervical dorsal root ganglion cells (Keller et al., 1985). It is likely that the central processes of the trigeminal neurons travel in the ventral part of the spinal trigeminal tract to terminate in the spinal trigeminal nucleus. Histological verification of extracellular recording sites in the spinal trigeminal nucleus show that vascular activated trigeminal neurons are located in the lateral half of layers III to V of MDH. However, central neurons that receive input from cerebral blood vessels have also been localized in Vr, Vc, and SVT remains (Dostrovsky et al., 1991). Reversible cold block of neural activity between the MDH and more rostral trigeminal subnuclei suggests that afferents from the cerebral blood vessels project directly to rostral and caudal trigeminal subnuclei (Davis and Dostrovsky, 1988a,b). It is thought that these afferents have an important role in mediating certain types of headache pain.

I. Orbital Afferents

1. Corneal

A study demonstrating transganglionic transport of HRP from the cornea in cats (Marfurt, 1981) revealed a sparse projection of primary afferent fibers from the cornea to the caudal part of Vp and mid-Vc, with more substantial projections to the perioibex region (caudal Vc and rostral MDH) and caudal MDH. At the level of caudal Vc, most of the reaction product was concentrated among the SVT remains. The MDH labeling was heaviest in layer IIa, with some projections extending into layers I and III. The most caudal projection, which extended to C-2, was distributed primarily in layer I of the spinal cord dorsal horn. These findings were essentially confirmed by Shigenaga et al., (1986a,b) following corneal injections of HRP in cats. More recently, Marfurt and Echtenkamp (1990) demonstrated a similar distribution of corneal afferents to the trigeminal nuclei in monkeys (Macaca fascicularis). It seems the cornea and other cutaneous tissues that are innervated mostly by small-diameter fibers may have some representation throughout the spinal nucleus, but the projections to the caudal part of Vr, the interstitial nucleus, and layers I and II of the MDH is greater.

2. Extraocular Muscle Afferents

In most species, afferent fibers to the extraocular muscles originate in trigeminal ganglion cells (Alvarado-Mallart et al., 1975; Porter and Spencer, 1982; Porter et al., 1983; Daunich et al., 1985; Porter, 1986; Ogasawara et al., 1987; Buisseret-Delmas and Buisseret, 1990; Porter and Donaldson, 1991). In the cat, some of these studies also advocate the presence of a minor contingent of afferent neurons in Vmes (Alvarado-Mallart et al., 1975; Buisseret-Delmas and Buisseret, 1990; Manni et al., 1987). The data regarding this contribution are inconclusive because of the high probability of the spread of tracer owing to the fact that the inferolateral boundary of the orbit in cats is formed by the internal pterygoid muscle. Studies assessing the central projections of extraocular muscle afferents implicate the spinal trigeminal nucleus as the primary muscle afferent recipient zone (Porter, 1986; Ogasawara et al., 1987; Buisseret-Delmas and Buisseret, 1990; Porter and Donaldson, 1991), although a second representation has been identified in the monkey cuneate nucleus. Interestingly, the extraocular projection to nucleus cuneatus partially overlaps the corresponding projection from dorsal neck musculature (Porter, 1986; Edney and Porter, 1986). Most authors identify the ventrolateral portion of Vr as an important afferent recipient zone for eye muscle afferents (Buisseret-Delmas and Buisseret, 1990; Porter and Donaldson, 1991), but the other subdivisions of Vr have also been implicated (Ogasawara et al., 1987; Buisseret-Delmas and Buisseret, 1990). Differences in opinion regarding the target subdivision(s) in the cat spinal trigeminal nucleus may be due to technical differences and the degree to which spread of tracer from the injection site was controlled. It is thought that most of the eye muscle afferents are involved in proprioceptive mechanisms (Porter and Donaldson, 1991). Proprioception in the extraocular muscles has been a controversial subject, both in terms of its anatomical substrate and the func-
tional use of information derived from eye muscle proprioceptors.

III. FUNCTIONAL REPRESENTATION

The patterns of primary afferent distribution with respect to the divisions of the trigeminal nerve and specific oral facial tissues provide the basis for considerations of functional representation within the trigeminal system. Four broad categories are discussed to consider some of the ways that new information regarding central projections of primary afferents have contributed to the evolution of existing concepts of functional representation.

A. Orofacial Pain and Temperature

Gerard (1923) and Sjöqvist (1938) were among the first to suggest that pain and thermal sensory experiences were products of information processing in more caudal parts of the trigeminal nucleus, whereas tactile information was represented in more rostral regions. Sjöqvist (1938) reported that sectioning of the tuberculum cinereum at the level of the obex produced relief from trigeminal neuralgia and an associated loss of ipsilateral pain and temperature sensibility in the skin and mucous tissues of the ipsilateral face; however, tactile sensibility was largely preserved. This surgical procedure severed the central processes of the most caudally projecting fibers in the spinal trigeminal tract. These and other early clinical observations (reviewed by Humphrey, 1969) that indicated a rostrocaudal modality segregation within the spinal trigeminal nucleus provided the focus for many experimental studies.

Recent studies involving tractotomy near the obex suggest that nociceptive fibers innervating intraoral structures (teeth, gums, tongue, etc.) terminate near the obex in the caudal part of the interpolar subnucleus (Young, 1982). These findings are in some respects supportive of the "onion-skin" distribution classically attributed to Dejerine (1914). Observations made in patients with syringobulbia, syringomyelia, or with posterior inferior cerebellar occlusion at slightly different levels led Dejerine to propose that primary afferent fibers that convey noxious stimuli from progressively more caudal and lateral regions of the face, in each of the three divisions of the trigeminal nerve, have progressively more caudal terminations below the obex (Figure 9).

![Figure 9. This illustrates the pattern of circumoral (5) intermediate (4,3,2) and peripheral (1) concentric facial zones according to Dejerine. Fibers that innervate the circumoral zone terminate near the obex, whereas intermediate and peripheral zones terminate more caudally in the subnucleus caudalis. The facial areas supplied by the major divisions of the trigeminal nerve are indicated. Figures 576 and 578 from the original article by Dejerine (1914) have been superimposed. (From Humphrey, in Kahn, Crosby, Schneider, and Taren (1969).)](image-url)

Although the role of Vc in orofacial pain and temperature mechanisms has been known for many years, the inability to identify cells that respond to noxious stimuli (Kruger et al., 1961; Wall and Taub, 1962) in early physiological studies was somewhat perplexing. However, a large number of tactile units could be identified in all parts of the spinal trigeminal nucleus, including Vc. One of the earliest reports of brain-stem unit activity in response to noxious stimuli was made by Eisenman et al. (1963). Interestingly, these responses to noxious stimuli were recorded from
cells located in rostral parts of the spinal trigeminal complex. They could not conclude that these were the products of primary afferent input, because ascending polysynaptic internuclear connections (Nasution and Shigenaga, 1987) could account for some of the observed responses. Neurons with specific responses to nociceptive stimuli were identified in Vc by Mosso and Kruger (1973). It is now clearly established that central neurons responsive to nociceptive specific (NS) stimuli, combinations of noxious and nonnoxious mechanical stimuli (wide dynamic range; WDR), and nonnoxious (low-threshold mechanoreceptive, LTM) stimuli occur in all regions of the spinal trigeminal nucleus (Dallel et al., 1988; Dubner et al., 1978; Hayashi et al., 1984; Hu, 1990; Sessle and Greenwood, 1976).

Layers I and IIa of the MDH and many of the interstitial cells are major contributors to the processing of nociceptive and thermal information. In particular, this part of the MDH is thought to be involved in the processing and projection of sensory-discriminative aspects of cutaneous facial pain. In general, small-diameter trigeminal afferents terminate in layers I and IIa and larger diameter fibers project to deeper layers (II to IV). Experimental studies have shown that many of the cells in layer I are nociceptive specific. However, WDR and LTM have also been identified in layer I. Layer V contains many WDR cells, LT cells, and a few NS cells. The intervening layers (II to IV) contain numerous interneurons. Neurons in this region that receive convergent inputs from muscle, joint, and cutaneous receptors are thought to provide the substrate for patterns of referred pain (Sessle et al., 1986). Similar patterns of convergence have been noted in more rostral parts of the spinal trigeminal nuclei and this region is also thought to be involved in pain referral mechanisms (Hayashi et al., 1985; Dallel et al., 1990).

Hayashi (1985b) showed that single high-threshold afferents terminated in Vc. In addition, Shulits and Light (1987) have confirmed projection of nociceptive primary afferents to interstitial cells located rostral to the obex. Other than a possible involvement in referred pain mechanisms, the function of more rostrally located nociceptive units has not been resolved entirely. It has been argued that the extensive pulpal representation in the rostral subnuclei may be related to prepain sensations or to spatio-temporal aspects of dental nociception (Marfurt and Turner, 1984).

A dual schema has been proposed for nociceptive input in the trigeminal system in which the rostral projection is primarily involved in oral pain and thermal sensations (including tooth pain) and projections caudal to the obex are primarily related to cutaneous pain and temperature (Azerad et al., 1982).

It is likely that most of the nociceptive units located rostral to obex receive collaterals from fibers en route to the MDH. Although it has been suggested that larger diameter pulpal afferents have a restricted projection to rostral trigeminal structures (Sugimoto et al., 1989), this point requires further study. When evaluating physiological data from extracellular recording studies of the trigeminal system, it is important to remember that nociceptive information may be relayed from caudal to rostral trigeminal regions by intrinsic connections within the spinal trigeminal nucleus (Nasution and Shigenaga, 1987) rather than from direct primary afferent input. In fact, there is evidence supporting a facilitative role for such connections (Dubner et al., 1978). It is now abundantly clear that primary afferent fibers from the tooth pulp project onto trigeminothalamic relay cells in the Vp and Vc (Sessle and Greenwood, 1976). A recent study of the effects of trigeminal tractotomy on thalamic nociceptive neurons (Dallel et al., 1988) showed that thalamic units activated by noxious stimuli to facial structures did not require an input to Vc. These results indicate that some of the nociceptive neurons from rostral nuclei relay their information to the thalamus in the manner of the traditional "sensory-discriminative" systems. However, a relatively small percentage of the NS and WDR units recorded in Vp project to thalamus (Hayashi et al., 1985). In addition, there is fairly good evidence that the more rostrally terminating nociceptive fibers from dental tissues are involved in orofacial reflexes (jaw-opening reflex; Mason et al., 1985).
B. Tactile Representation

The trigeminal sensory nuclear complex receives significant input from tactile mechanoreceptors. Extracellular recording studies by Kruger and Michel (1962a,b,c) and Eisenman et al. (1963) demonstrated that all facial regions were represented throughout the rostrocaudal extent of the trigeminal sensory nuclei. Oral cavity representation was medially located and cutaneous structures were more laterally situated. However, not all facial regions were equally represented at all levels of the trigeminal complex. Regional differences in representation were attributed, in part, to differences in innervation density of the peripheral structures.

Although most early studies emphasize the loss of cutaneous pain and temperature representation subsequent to tractotomy at the obex, there is also some impairment of tactile sensibility following this procedure (Mosso and Kruger, 1973; Brodal, 1981). As discussed earlier, neurons with tactile receptive fields are common in Vc. Primary afferent endings from small-diameter myelinated axons terminate in layers II and III and larger myelinated primary afferent fibers that are likely to be involved in transmission of mechanoreceptive stimuli terminate in layer IV of the MDH (Gobel and Hockfield, 1977).

Hayashi (1985a,b) suggested that more rostral regions of the trigeminal complex were organized in such a way that in rodents and cats the terminal arbors of vibrissae and facial mechanoreceptive afferents terminated laterally, whereas tooth and other intraoral afferents arborized medially. This morphological pattern would be consistent with physiological data that supported the medial representation of intraoral neurons responsive to tactile stimuli in cats (Eisenman et al., 1963).

The most common type of physiologically defined neurons observed in Vi have small receptive fields that respond best to low-threshold mechanoreceptive stimuli, but neurons that respond to noxious stimuli have also been documented in this region. There is also a significant population of neurons with convergent receptive fields from cutaneous, intraoral, and muscle afferents in Vc (Hayashi et al., 1984). Most neurons in Vi respond to cutaneous mechanical stimuli (Eisenman et al., 1963; Kruger and Michel, 1962a,b,c). More rostral nuclei in the trigeminal complex, including Vp, Vpd, and Vpv, also contain cells with tactile receptive fields. However, the organization of Vp has been shown to be relatively complex (Shigenaga et al., 1986b) and includes an extensive representation for intraoral structures. Both physiological and morphological data suggest that, in addition to providing a relay for the most discriminative types of tactile sensation from the face, Vpd relays similar types of sensory information from within and around the oral cavity.

C. Mandibular Kinesthesia

Kinesthesia, in the broadest sense, refers to the awareness of the position and movements of the limbs and other body parts whether self-generated or imposed externally. Contributions from temporomandibular joint receptors in kinesthetic functions has been predicated by studies of joint afferents in the trigeminal ganglion (Lund and Matthews, 1981). The relatively few studies addressing the central processing of kinesthetic signals from the temporomandibular joint suggest that afferent projections to the rostral trigeminal sensory nuclei participate in signaling jaw position. Kawamura and Abe (1974) identified movement-activated neurons with rapidly and slowly adapting properties. These were located in Vp and in Vc. These responses were thought to result primarily from activation of joint afferents because the joint was surgically isolated from surrounding structures. Neurons in Vsup (Jerge, 1963b), adjacent areas, and in Vp that are either activated or inhibited by jaw movements have been described by Eisenman et al. (1963). Because these observations were made in surgically intact experimental preparations (i.e., without isolating specific nerve fibers and/or deep tissue receptive fields), the precise receptive fields of the identified neurons could not be determined in either study. Jerge reported that neurons in the cat supratrigeminal region receive convergent information from orofacial structures. However, a direct projection from the temporomandibular joint to an area outside the boundaries of Vp or Vc in a supratrigeminal region was not confirmed.
by transganglionic transport studies (Capra, 1987). Further studies are required to define the specific mechanoreceptive functions of joint receptors and the sites where such information is processed.

Although temporomandibular joint receptors are probably involved in detecting changes in jaw position, recent evidence suggests muscle receptors may play a more important role in kinesthesia than joint receptors (Clark et al., 1985; Goodwin et al., 1972a,b,c). Observations that hair, skin, and mucosal receptors are often activated during jaw movement suggest that they may participate in kinesthetic functions and also contribute to regulation of chewing behavior (Appenteng et al., 1982a,b; Rossignol et al., 1988), but their precise contribution to such activities requires further study.

Central pathways involved in the relay of information from low-threshold muscle afferents to the cortex have been described for the upper and lower extremities (Weisendanger and Miles, 1982), but relatively little information is available regarding the central processing of kinesthetic information originating from receptors in masticatory muscles and other orofacial tissues. Recent studies in our laboratory have demonstrated a number of movement-sensitive central neurons that receive masseter muscle afferent input and nonmuscle movement-related afferents in caudal V₁. Antidromic stimulation shows that many of the cells in this region project to the contralateral thalamus (Hayashi et al., 1984). Thalamic projections from V₁ have been documented by retrograde tracing studies with HRP (Yasui et al., 1983). Many of the trigeminothalamic neurons respond to passively imposed jaw movements (N.F.C., unpublished observations).

It has been suggested that on the basis of cellular architecture and central projections, a possible homology exists between the cuneate nucleus and V₁ neurons (Shigenaga et al., 1986b). Experimental data have shown the convergence of cutaneous and proprioceptive input from upper extremity muscles onto cuneate neurons. Many of these cuneate cells were muscle spindle-driven neurons with thalamic projections (Millar, 1979) and they may play a role in limb kinesthesia. Neurons in the adjacent region of V₁ that respond to jaw movements and have convergent receptive fields may be likened to such cuneate neurons and may contribute to mandibular kinesthesia.

D. Motor Control

Significant light can be shed on the role of primary afferent fibers in the control of movement by viewing them with respect to several recent issues in motor control.

1. Axonal Morphology

It is difficult to look at the reconstructed axons from intracellular staining studies without wondering how the afferent impulse might be conducted within the axonal arborization. Waxman (1975) has argued that axons can perform a variety of integrative functions depending on their geometry. Experimental evidence corroborates this hypothesis by showing that axons may function as simple transmission lines, delay lines, or may conduct afferent impulses intermittently (Deschênes and Landry, 1980; Grossman et al., 1979).

In the trigeminal segmental motor system, it has become increasingly important to consider the possibilities of information processing within the primary afferent axon. Miyazaki and Luschei (1987) reported that some of their recordings from V₁ were phase shifted with respect to jaw displacement. It is interesting to speculate whether the phase shifting was due to synaptic integration on second-order cells or if it resulted from delay-line characteristics in primary afferent axon collaterals.

In the cat hind limb, group Ia afferents enter the spinal cord and bifurcate into a rostral and caudal branch with the diameter of the caudal branch being smaller than the ascending branch (Ishizuka et al., 1979). In the trigeminal system, the size discrepancy between the ascending and descending branches of mesencephalic primary afferent axons can be quite pronounced at the junction between the peripheral process, the process that extends rostrally into the tract of the mesencephalic nucleus, and the process that projects caudally into the tract of Probst (Figure 10; also Luo et al., 1991; Shigenaga et al., 1988b,
1989, 1990a). The diameter of the branch projecting into the tract of the mesencephalic nucleus is often larger in diameter than that branching into the tract of Probst (Dessem and Taylor, 1989a; Shigenaga et al., 1990a), suggesting that the safety factor for afferent impulses conducting into the tract of Probst is higher than that into the mesencephalic tract. Impulses propagated into both tracts would be expected to have a much slower conduction velocity in the tract of Probst because of the smaller fiber diameter. Similar morphological characteristics need to be considered at branch points for axon collaterals.

In the spinal cord, Lüscher (Lüscher, 1990; Lüscher et al., 1979, 1983a,b) suggested that the invasion of Ia terminals is a graded process that is generally more complete in the axonal arborizations to small spinal motoneurons because of fewer branch points. This group of investigators has, therefore, implicated branch-point failure as a mechanism contributing to the size principle. It will be important to test this hypothesis physiologically and anatomically in the trigeminal system and to determine whether branch-point failure is a significant processing mechanism in the trigeminal system.

The data of Lüscher (Lüscher, 1990; Lüscher et al., 1979, 1983a,b) also suggest the existence of inactive synapses on spinal cord primary afferent fibers. It is important to keep in mind when considering the distribution of primary afferent synaptic boutons that connectivity may not be static. Clearly, further investigations into the integrative properties of trigeminal primary afferent axons are needed to understand the relationship between axonal morphology and afferent impulse conduction.

2. Sensory Partitioning

A number of studies have demonstrated that the nervous system is capable of controlling different portions of a single anatomical muscle independently (English, 1984; Herring et al., 1979). Because the fiber orientation of muscles of mastication is quite complex, perhaps it is not surprising that differential control exists in these muscles (Blanksma and Van Eijden, 1990; Herring et al., 1979). Recent studies in cat hind-limb muscles have shown that in addition to differential control of efferent output, muscle reflexes can be localized within a single muscle (Cameron et al., 1981). This has led Binder and Stuart to propose a "partitioning" hypothesis (Binder et al., 1977; Stuart and Binder, 1977).

In the trigeminal system, considerable electrophysiological and anatomical studies in animals have shown that the projection of jaw-muscle spindle afferents is restricted to a small region of V mes (Appenteng et al., 1978; Dessem and Taylor, 1989a; Nozaki et al., 1985; Shigenaga
et al., 1990a). Smith et al. (1985), however, examined the distribution of reflex responses to tapping the human jaw muscles and found no evidence for localization of the reflex responses, although it is possible that the tap stimulus was not confined to a restricted portion of the test muscles (see footnote in Stuart et al., 1988). In contrast to this, Amano and Yoneda (1980) showed evidence suggesting that the reflex effects of tooth displacement on the firing of single motor units is concentrated in portions of the human masseter muscle.

It is also not known whether any of these reflexes are focused onto a particular motoneuron type. It has been suggested that in the cat (Appenteng et al., 1978), the restricted distribution of jaw-muscle spindle afferents is onto small, presumably type S, motoneurons and is involved in the postural regulation of the jaw. Future studies of the central distribution of trigeminal primary afferents should be useful in clarifying the features, extent, and functional significance of sensory partitioning in the trigeminal system.

a. Primary Afferent Projections to Interneurons

Considerable progress has been made in determining the location of interneurons that receive primary afferent input and project to V_{mot} (Appenteng et al., 1989; Landgren and Olsson, 1976; Nakamura et al., 1976; Olsson et al., 1986; Shigenaga et al., 1988c; Mizuno et al., 1983). Substantial evidence indicates, for instance, that cells in the supratrigeminal region receive convergent trigeminal sensory inputs and are involved in short latency pathways to the trigeminal motor nuclei (Kamogawa et al., 1988; Luo et al., 1991). However, the strength of synaptic input from specific modalities to these and other trigeminal interneurons is not well understood. Evidence from intracellular staining studies suggests that synaptic boutons from muscle spindle afferents are more numerous in the supratrigeminal region than in V_{mot} but are smaller in size (Dessem and Taylor, 1989). Because there is some evidence that larger terminals release a greater amount of transmitters and have larger postsynaptic effects than smaller terminals (Kuno et al., 1971, 1973), it will be important for future studies to determine the size and location of primary afferent boutons on interneurons.

Systematic classification of trigeminal interneurons, based on afferent input, comparable to the 1a and 1b interneurons found in the spinal cord is still lacking. It seems likely that many trigeminal interneurons are shared by various reflex pathways (Appenteng et al., 1989, 1990; Gura et al., 1972; Kamogawa et al., 1988; Olsson et al., 1986; Sessle, 1977a) as in the spinal cord (Harrison et al., 1983; Jankowska et al., 1981).

3. Central Modulation of Trigeminal Primary Afferent Input

Trigeminal primary afferent input may be modified not only by integration within the axonal arborization, as discussed earlier, but potentially by presynaptic mechanisms, synapses on the primary afferent cell bodies, and via electrotonic junctions between primary afferent cells.

Presynaptic mechanisms have been implicated recently in the phasic modulation of primary afferent input. In humans, presynaptic mechanisms have been proposed to account for the phasic modulation of the H-reflex during locomotion (Capaday and Stein, 1986, 1987). The phasic modulation of cutaneous reflexes in cats has been attributed to presynaptic mechanisms (Drew and Rossignol, 1985, 1987; Dubuc et al., 1988; Gossard et al., 1989). In the trigeminal system, primary afferent depolarization has been demonstrated directly (Browne and Goldberg, 1978a; Yu and Avery, 1974) and implicated in the modulation of trigeminal interneurons and reflexes (Browne and Goldberg, 1978b; Goldberg, 1972; Goldberg and Browne, 1974; Nakamura and Wu, 1970). In the jaw-opening reflex, the phasic modulation that occurs during mastication (Kurasawa et al., 1988; Lund and Rossignol, 1981; Lund et al., 1981, 1983, 1984) may be controlled by presynaptic gating of primary afferent input (Lund et al., 1981).

The presence of synaptic input directly onto the cell bodies of primary afferents in V_{mot} allows the possibility of a unique form of primary afferent modulation. These synapses theoretically
could produce centrifugal impulses in the afferent axon that would block primary afferent input and could also invade the primary afferent axonal arborization. It has been suggested recently that this synaptic input onto $V_{\text{mes}}$ cells is responsible for the phasic modulation of jaw-muscle spindle afferents during fictive mastication (Kolta et al., 1990).

Electrotonic coupling, via gap junctions, between cells in the $V_{\text{mes}}$ must also be considered as a possible mechanism for the modulation of trigeminal primary afferent input. Baker and Llinás (1971) demonstrated that activation of some $V_{\text{mes}}$ axons could invade adjacent coupled cells and generate action potentials. Mechanisms such as these could produce centrifugal impulses and block primary afferent input.

IV. IMMUNOCYTOCHEMISTRY OF TRIGEMINAL PRIMARY AFFERENT NEURONS

Immunocytochemical methods have been used to determine the distribution of putative neurotransmitters and neuromodulators in trigeminal primary afferents and their sites of central termination. Comparisons of neuropeptide distribution in MDH and the spinal cord dorsal horn have added to the criteria supporting the homology between these regions. Much of this work has been concerned with determining the distribution of substance P (Priestley et al., 1982), a peptide known to be involved in nociceptive pathways. Primary afferent terminals with substance P-like (SP) immunoreactivity have been identified in MDH and among the interstitial cells of rodents. These regions, which receive nociceptive specific information, also contain numerous other substances implicated in nociception and reflex modulation. Positive staining has been shown for $\gamma$-aminobutyric acid-like (GABA), serotonin-like (5-HT), and enkephalin-like (Enk) immunoreactivity as well as other neuropeptides (Matthews et al., 1989). It is likely that further studies and novel approaches will continue to facilitate our understanding of structure-function relationships in the trigeminal system.

A. Substance P

Histochemical processing of primary afferent fibers for substance P-like immunoreactivity (SP) reveals a similar distribution in the spinal cord dorsal horn and in MDH of rats (Priestley et al., 1982). Immunoreactivity in MDH was found in axonal varicosities that were presynaptic to dendrites and somata in layers I and II or confluent with other immunoreactive and nonimmunoreactive axons. The heaviest projections in the rat were to layer I and the outer two thirds of layer II. The projections to deeper layers are lighter (Priestley et al., 1982). Synaptic glomeruli is one of the more striking ultrastructural features in the substantia gelatinosa of both the spinal cord dorsal horn and MDH. These glomeruli consist of central axonal boutons of known primary afferent origin surrounded mainly, but not exclusively, by axodendritic contacts. Three types have been defined using several morphological or functional criteria of the central bouton and include the type I, IIA, and IIB. The type I glomerulus has a dark sinuous central varicosity. It is capsaicin sensitive, and some 80% of these are acid phosphatase positive. SP is found in a large number of type I synaptic glomeruli.

SP-containing varicosities have both round agranular vesicles and a certain number of large granular vesicles in rat, cat, and monkey. The distribution of SP near large granular vesicles and localization of immunoreactivity both near and away from the synapse suggest that synaptic and nonsynaptic release of SP may occur. Terminal varicosities are usually apposed to large and medium-sized dendrites in layer I and the I/II border. It is likely that many of the terminals in layer I occur along trigeminothalamic neurons, whereas in layer II, varicosities are distributed to the interneurons (e.g., islet cells described by Gobel and Hockfield (1977). Excellent descriptions of the potential interactions between SP, other peptides, and putative neurotransmitters intrinsic to
the CNS have been considered in reports of the primary afferent distribution of SP (for discussion and additional references, see Priestley et al., 1982; Ribeiro-Da-Silva et al., 1989). A schematic depiction summarizing the distribution of SP terminals in MDH adapted from Priestley et al. (1982) is shown in Figure 11.

B. Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide-like immunoreactivity (CGRP) has been localized in a large proportion of small- to medium-diameter sensory ganglion cells whose central terminals are distributed in the medullary dorsal horn. An important feature of CGRP is that it is thought to occur only in primary afferent fibers. In the periphery, there are significant levels of CGRP in the tooth pulp of rat, cat, and monkey (Silverman and Kruger, 1987). There is a broad, if not total, overlap between fiber populations containing SP and CGRP. Processes in the central nervous system that contain both SP and CGRP are likely to be primary afferent fibers, whereas fibers reactive only to SP may be processes of intrinsic

![Diagram of Substance P (SP) terminals in the medullary dorsal horn.](image)

**FIGURE 11.** This illustrates the relationship of Substance P (SP) immunoreactive terminals to various neuronal elements in the medullary dorsal horn. Lines indicate probable connections. Four sites of termination are indicated (1–4). (1) Synapses on large marginal neurons (Mg) in layer I. Some of these are projection neurons. (2) Synapses on substantia gelatinosa (SG) interneurons in layer II. (3) Synapses on a second class of interneurons that are likely to be the "islet cells" described by Gobel and Hockfield (1977). (4) Synapses in which SP terminals are postsynaptic to other unstained terminals. The diagram also shows four possible ways (a–d) in which enkephalinergic neurons (stippled) may interact with SP. (a) Synapses by enkephalin immunoreactive terminal on marginal zone neurons. (b) Synapses by enkephalin immunoreactive terminal onto SG interneurons that receive SP inputs. (c) Synapses by SP immunoreactive terminal onto enkephalin containing islet cells. (d) Axoaxonic synapses between enkephalin and SP immunoreactive terminals. I and II indicate laminae I and II and T indicates transmission cells. (Adapted from Priestley et al., J. Comp. Neurol., 211:31–49 (1982). With permission.)

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(central) neurons. Loss of CGRP in the peripheral terminals of nerve fibers after sectioning of the inferior alveolar nerve (Silverman and Kruger, 1987) led to the proposal that this substance and other neuropeptides may mediate important efferent functions (e.g., peripheral vasodilatation). This is an extremely important concept because it suggests that primary afferent nerve fibers serve important actions in peripheral tissues in addition to their assumed sensory functions.

C. Other Histochemical and Immunohistochemical Markers

Quantitative studies on rat dorsal-root ganglion cells show that SP neurons comprise only 10% to 20% of the small cell population and that 60% to 75% of the total dorsal-root ganglion-cell population is made up of small neurons (Alvarez et al., 1989). Of the remaining primary afferents, some stain positive with fluoride-resistant acid phosphatase histochemistry (FRAP) and others show somatostatin-like immunoreactivity (SOM). Fluoride-resistant acid phosphatase staining is somewhat diffuse, and SOM staining has been demonstrated in a number of intrinsic fibers that overlap in distribution with primary afferents. Ganglion cells that project to inner layers of the spinal dorsal horn that apparently do not show overlap with CGRP-containing neurons have been shown to contain FRAP (Silverman and Kruger, 1988). Ultrastructural studies show that, in contrast to SP immunoreactive terminals, acid phosphatase-positive varicosities contain few large, dense vesicles (Priestley et al., 1982).

Some ganglion cells express unique oligosaccharide markers on their surface. The monoclonal antibodies LD2 and LA4 are antiglycoconjugate antibodies that stain two practically nonoverlapping subpopulations of small DRG cells. Furthermore, these are different from the SP-containing cell population. Staining is prominent in both the axons and terminals, so that this can be used to trace the central projections of these cells. A subpopulation of LD2 immunoreactive cells also expresses SOM and most LA4 immunoreactive cells (>75%) contain FRAP. Some glial cells also show immunoreactivity to LA4.

It is possible to subdivide layer II primary afferent terminations on the basis of immunohistochemically defined oligosaccharide membrane markers. The distribution of immunoreactivity for both LD2 and LA4 antibodies is broadly similar to the distribution of small-diameter primary afferents mapped using capsaicin-evoked degeneration. Capsaicin has a marked effect on SP-containing neurons. Unlike CGRP and SP, which have both been identified in more rostral regions of the trigeminal nuclei, LD2 or LA4 was not found outside of MDH. Capsaicin-sensitive fibers, presumably SP-containing, have been identified in V1 and it is known that this region receives some input from the cornea and tooth pulp. The distribution of LD2 immunoreactive fibers in the outer part of layer II is similar to that of the peptide-containing fibers, but, in contrast to the peptides, LD2 is not common in layer I (Alvarez et al., 1989).

D. Nerve Growth Factor

Fibers that demonstrate nerve growth factor receptor-like immunoreactivity (NGFR) have also been identified in MDH (Fried et al., 1990). All of these fibers contain CGRP, but some CGRP fibers do not contain NGFR. The distribution of both CGRP and NGFR was heaviest in layers I and IIa. Labeling in IIa was less intense in the cat when compared with the monkey. Moderate NGFR activity was also observed in layer III, although very little CGRP was reported in this layer (Fried et al., 1990). Essentially, the distribution of NGFR activity is similar in cat, monkey, and the rat (Fried et al., 1990). Of interest to the earliest consideration of vascular innervation, cerebral vessels showed NGFR reactivity leading to the suggestion that these fibers probably project to MDH.

E. Carbonic Anhydrase (CA)

The enzyme carbonic anhydrase has been demonstrated in large neurons of dorsal-root ganglia and their fiber processes. It has been proposed that CA-positive fibers may be a characteristic feature of large-diameter muscle afferents.
(Szabolcs et al., 1989). Demonstration of CA may be useful in determining the distribution of low-threshold muscle afferents in the trigeminal system. Sugimoto et al. (1989) used retrograde transport of FITC-labeled lectins combined with CA histochemistry. The rationale was that CA would serve as a natural marker for large-diameter afferents. The results of the study suggest that many pulpal afferents, (i.e., those that were fluorescent and CA positive) had relatively large somata. The larger perikarya are typically associated with peripheral fibers in the A-β size category. It was proposed that the large double-labeled somata were pulpal afferents and that they account for the more rostral pulpal projections to V_o and V_p. There is some concern regarding the validity of this observation, because the authors apparently did not control for spread of tracer to the periodontal ligaments either by examining the injection site or searching V_mes for labeled perikarya. It was clear that they did not accept the possibility that the pulp might have some input from V_mes. There is a potential that, under some circumstances, carbonic anhydrase activity can provide a useful marker for larger-diameter fibers.

V. CONCLUSIONS AND FUTURE DIRECTIONS

A review of the distribution of primary afferent somatosensory projections that innervate oral and facial tissues reveals the rapid transition from our ability to make general observations of somatotopic organization of these fibers to very specific morphological details of single physiologically identified fibers along with the neurochemistry of this region. These studies contribute to our understanding of the function of these projections in sensory and motor mechanisms and provide the basis for sophisticated studies of development and plasticity in the somatosensory system.

The proposed homology between the outer layers of MDH and the outer layers of the spinal cord dorsal horn has been strengthened by single-fiber labeling studies and by immunocytochemical studies of this region. In addition, transganglionic studies support early observations that this region is organized in such a way that there is a concentric or “onion skin” pattern of facial representation for pain and temperature. The most rostral parts of the MDH receive input from peri-oral regions, whereas progressively more caudal parts of MDH receive inputs from more lateral facial regions.

In addition to the detailed cutaneous representation of nociceptive afferents in MDH, recent experiments have amply confirmed the presence of a significant nociceptive input to neurons in the rostral parts of the spinal trigeminal nucleus. Many of the latter are pulpal afferents. Both MDH and more rostral neurons that receive these afferents have thalamic projections and may participate in sensory-discriminative functions.

In addition to the concentric pattern for nociceptive cutaneous afferents in the outer layers of MDH, trigeminal primary afferents provide a columnar representation of all facial regions throughout most of the spinal trigeminal nucleus. However, not all peripheral structures are represented (i.e., have the same innervation density) equally throughout the entire rostrocaudal extent of the nucleus. Regional differences appear to be related at least in part to considerations of functional specialization (e.g., a primary role of corneal receptors in nociception is associated with a predominant peri-ocular representation). However, modality specificity of these columns is not required nor has it been proven.

Although V_p shares some properties of the dorsal column nuclei, the two are not completely homologous. A similar conclusion may be inferred with respect to homology between regions of V, and the spinocerebellar pathways. It is suggested that additional efforts to establish such homologies are purely academic in nature.

The trigeminal mesencephalic nucleus is not only unique among primary afferent neurons since it is located within the CNS, but also because it contains first-order pseudo-unipolar and multipolar cells that are subject to synaptic modulation at their cell bodies. Furthermore, the central connections of the mesencephalic trigeminal cells are extensive, suggesting that they play a much more complex role than merely providing the afferent limb of the jaw-closing reflex.

Reconstruction of the terminal arbors of single physiologically identified neurons, reveals that vibrissae and other large-diameter mechanore-
ceptive ganglion cell afferents have a similar morphology regardless of their site of termination in the spinal trigeminal nucleus. However, there are differences in the spatial distribution of these arbors in each subnucleus. In addition, the morphology of the terminal arbors of large- and small-diameter myelinated fibers seems to be quite different.

Although gathering data describing the morphology of terminal arbors for different classes of afferents is a time-intensive endeavor, it will greatly advance our understanding of the anatomical substrate for brain-stem sensory and motor mechanisms. Issues related to signal processing, imposed by the structure of trigeminal primary afferent neurons, may be answered with a better knowledge of single-fiber morphology. Specific examples include determining the extent to which branch point failure may affect the transmission of trigeminal afferent impulses and how differences in the diameter of primary afferent collaterals affect delay-line characteristics of primary afferent fibers.

Continued efforts should be made to further our understanding of the central modulation of trigeminal primary afferent neurons through presynaptic inhibition and to define the role of presynaptic mechanisms in perception and in the phasic modulation of trigeminal reflexes.

Further studies to determine the precise functional role of rostral neurons that receive nociceptive inputs from the tooth pulp and other orofacial structures may help provide insights as to how nociceptive information may alter patterns of motor behavior (Lund et al., 1991).

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ABBREVIATIONS

Brainstem structures:

Interstitial system of the spinal trigeminal tract — SVT
Interstitial trigeminal nucleus — V
Medullary dorsal horn — MDH
Parvocellular reticular formation — PCRF
Principal sensory nucleus — Vp
Principal sensory nucleus, dorsal subdivision — Vpd
Principal sensory nucleus, ventral subdivision of the — Vpv
Probst tract P1
Spinal nucleus of the trigeminal nerve — VSN
Subnucleus oralis — Vo
Subnucleus interpolaris — Vi
Subnucleus caudalis — Vc
Supratrigeminal nucleus — Vsup
Trigeminal mesencephalic nucleus — Vmes
Trigeminal motor nucleus — Vmot

Immunohistochemical:

CA — carbonic anhydrase
CGRP — calcitonin gene-related peptide-like
FRAP — fluoride resistant acid phosphatase-like
GABA — y-aminobutyric acid-like
NGFR — nerve growth factor receptor-like
SOM — somatostatin-like
SP — substance P-like

Peripheral structures:

Temporomandibular joint-TMJ
Trigeminal ganglion — TG
Trigeminal nerve — V

Other:

Horseradish peroxidase — HRP
LTM — low threshold mechanoreceptive
NS — nociceptive specific
WDR — wide dynamic range
REFERENCES


Berkovitz, B. K. B., R. C. Shore, and B. J. Moxham: The Occurrence of a Lamellated Nerve Terminal in the Per-
Bernick, Binder, Brashear, Byers, Brown, 42
Browne, Byers, Byers, of Wisconsin physiol.
Connections: Enzymatic Berveuses
Berveuses Neurol.
poromandibular
Mechanoreceptors
nucleus
Nonnociceptive
robiol.
ger-Verlag,
Neurol.

geminal

Types
ofCat:
250:181-191
231:500-518
25:39-93
279:117-127


Jacquin, M. F., N. L. Chiaia, and R. W. Rhoades: Trigeminal Projections to Contralateral Dorsal Horn: Cen-


Kurasawa, I., Y. Hirose, T. Sunada, and Y. Nakamura: Phase-linked Modulation of Excitability of Presynaptic Terminals of Low-threshold Afferent Fibers in the In-


Marfurt, C. F. and D. F. Turner: The Central Projections of Tooth Pulp Afferent Neurons in the Rat as Determined


