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Review Article

Morphofunctional Organization of the Oromotor Nuclei of the Rat Brain

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Abstract

This article will describe the internal organization of the motor nuclei of the trigeminal (Mo5), facial (7) and hypoglossal (12) nerves and identify the sources of central projections to them. Brainstem projections to these nuclei arise from structures in both the sensory and reticular formations and mediate a wide range of oral-related behaviors that range from simple oral reflexes, such as the disynaptic jaw opening reflex, to complex oral functions, such as swallowing, chewing and breathing.

Keywords: Morphofunctional organization; Oromotor nuclei; Rat; Brain

Introduction

Although it is believed that swallowing, chewing, licking and breathing are provided by central generators of impulse activity of the brain stem, which are necessary for the coordinated transmission of signals to the corresponding oromotor areas [1]. In addition to receiving excitatory and inhibitory signals using classical neurotransmitters, the oromotor nuclei also receive signals using various neuromodulatory substances. The intrinsic membrane properties of motoneurons, as well as the colocalization of neuromodulators, provide the potential for further patterning of motor activity. γ-aminobutyric acid, calcitonin gene-related peptide, urotensin II and urocortin have been localized within oromotoneurons, and cholecystokinin mRNA has also been identified [1,2]. An even greater number of interneurons are contained in the oromotor nuclei within 12 with axonal collaterals in Mo5 and, in species other than rats, central projections originating from Mo5 and 7 [2]. Although each of the oromotor nuclei has unique characteristics, the coordination between the muscles innervated by Mo5, 7, and 12 during feeding, grooming, and respiration is perhaps the most compelling reason to discuss the neuroanatomy of these nuclei within the scope of this article.

Motor Trigeminal Nucleus

Intrinsic Organization

Myotopic Organization

The rat trigeminal motor nucleus is conventionally divided into a large dorsolateral part defining the rostrocaudal length of the nucleus, and a smaller ventromedial part in the caudal two-thirds. Although the accessory nucleus for Mo5 has been labeled using peripheral nerve cobalt labeling, these neurons almost certainly correspond to the ventromedial division of the principal nucleus rather than motoneurons outside the principal nucleus [3].

The muscles that close the jaws—masticatory (superficial, Ms; deep anterior, Ma), Temporal (T) and medial (external) Pterygoid (Pm)—are innervated from the Dorsolateral Region (DL); the jaw opening muscles, the Anterior Digastric (AD) and Mylohyoid (MY), are innervated from the ventromedial division (VM). The third jaw-opening muscle, the lateral (internal) Pterygoid Process (Pl), is grouped with the jaw-closing motor neurons in the ventral dorsolateral region. In rats, the location of medial and lateral pterygoid motoneurons was not localized individually within the DL; however, the medial pterygoid motoneurons are located either ventral or lateral to the lateral pterygoid motoneurons. Laminar organization further determines the distribution of motoneurons within the DL [3]. The motor neurons innervating the deep masseter anterior muscle are located between the motor neurons innervating the superficial masseter muscle further laterally and the temporalis muscle dorsomedially.

The various “compartments” or “anatomical partitions” of the rabbit masseter muscle function with some degree of independence during chewing. Spatial separation of the motoneurons innervating these different compartments potentially allows for segregation of input signals as a source of differential activation. However, the extent of motoneuron separation is unclear. Superficial masseteric motor neurons occupy a dorsolateral position in the dorsal division compared with deep masseteric motor neurons, which are located more medially [4]. The overlap between these two neuronal populations was on

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the order of 50%. In contrast, after applying individual fluorescent tracers to different nerve branches, the overlap between deep and superficial masticatory motor neurons was estimated to be more than 90%. Motor neurons innervating the transverse mandibular muscle were not specifically localized in rats, but were grouped together in the same area as motor neurons innervating the superficial masseter muscle of the guinea pig.

In the ventromedial portion of Mo5, the anterior digastric motoneurons are located dorsomedial to the mylohyoid motoneurons. Innervation manifests itself strictly ipsilaterally. Evidence that a small number of Mo5 neurons innervate the contralateral AD has not been confirmed. The tensor palati muscle is also innervated by ventromedial motor neurons [5].

In rats, the tensor tympani muscle is innervated by trigeminal motoneurons located ventral to Mo5 and medial to the exiting trigeminal roots and thus appears at approximately the same anatomical location as group k neurons. Group k neurons represent a cell column outside the cytoarchitectonic boundaries of Mo5 and contain (additional) motor neurons innervating the masseter and anterior digastric muscles. Group k motoneurons are smaller than those in Mo5 and reflect the topology observed in the main nucleus, i.e., the masticatory motoneurons are located dorsal to the digastric motoneurons [3,4]. However, there are few references to group k in rats, and group k innervation of the masseter and digastric muscles has not been described.

Cytoarchitectonics

Each Mo5 contains approximately 2265 to 2979 cells, most of which innervate the jaw closing muscles. The dorsolateral region contains multipolar cells of both small (8–14 μm) and large (28–42 μm) diameters, which correlates with a bimodal distribution of nerve fiber diameters. Muscle spindles in the rat jaw closing muscles may terminate on small (presumably) γ-efferent motoneurons in dorsolateral Mo5. Two classes of multipolar cells in the ventromedial compartment are also clearly visible, although large cells (24–34 μm in diameter) are not as large as their dorsolateral counterparts and small cells (16–20 μm in diameter) are not as small [1,4]. The absence of very small neurons in the ventromedial compartment is consistent with the absence of muscle spindles in the jaw opener muscles. Axosomatic synapses cover, on average, 78% of the cell bodies of large multipolar Mo5 cells, in contrast to smaller multipolar or spindle cells, which have proportionally much fewer synapses.

In addition to body size, intracranial axonal trajectory further differentiates dorsolateral and ventromedial cells. The axons of the dorsolateral division emerge directly from the brain, forming several large roots that pass ventral to the main sensory nucleus of the trigeminal nerve (Pr5). However, the axons of the ventromedial division first run dorsally, forming the rostral genu to the more prominent genu of the facial nerve (7n), and then turn ventrolaterally as a separate root, parallel to the fibers of the dorsolateral division. Although classical descriptions of trigeminal motoneurons do not include axonal collaterals, collaterals have been observed for each of four Mo5 cells filled intracellularly with Horseradish Peroxidase (HRP). For three of the four cells, the motor neuron output axon branches within Mo5, and the fourth axon branches within Pr5 [1,3]. Unfortunately, no other intracellular labeling studies have reported axonal collaterals, which makes their existence controversial questionable.

Like all cranial motor nuclei, Mo5 is cholinergic. In addition, Calcitonin Gene-Related Peptides (CGRP), urotensin II and urocortin are localized in Mo5 cells. Cholecystokinin (CCK) messenger RNA has also been widely reported; however, there is little evidence for immunohistochemical detection of the peptide.

Dendritic Architecture

The dendrites of neurons located in the center of Mo5 extend from the cell bodies symmetrically compared with cells located more peripherally, with the dendrites diverging predominantly into the nucleus or following the contour of the nucleus. Dendrites are mainly concentrated in the nucleus; however, several jaw-closing motoneuron dendrites extend dorsally and laterally beyond the boundaries of Mo5 into the Mesencephalic trigeminal nucleus (Me5), principal trigeminal nucleus (Pr5), and supra- and intertrigeminal areas or medially into the pontine reticular formation. The dendrites of the motoneurons innervating the extraoral muscles do not overlap the dendritic fields of the orally connected motoneurons of the trigeminal nerve. Thus, the dendrites of tensor tympani motoneurons do not overlap the dendritic or somatic fields of nearby jaw-closing or opening motor neurons, but are in close proximity to the superior olive, providing a possible substrate for auditory reflex function [3,4]. Quantitative ultrastructural analysis of synapses on masticatory motoneurons showed a differential distribution such that putative inhibitory synapses were predominantly distributed on proximal dendrites.

Interneurons

A class of small spindle-shaped neurons located predominantly around the boundaries of Mo5 and having few synaptic terminals may be interneurons. Other, presumably non-motoneuronal cells within Mo5 have central projections. Cells within Mo5 have been labeled retrogradely by injections of HRP into the cerebellum, and projections from Mo5 to the hypoglossal nucleus have also been reported [5,6]. In addition, a small projection of neurons in the jaw closure region Mo5 to a homologous region on the contralateral side may contribute to bilateral jaw closure.

Afferent Projections

Forebrain Pathways

Although there is little anatomical evidence for direct Mo5 projections to the forebrain in rats based on retrograde or anterograde tracers, this view may need to be modified. Recent work in cats suggests direct projections from hypothalamic orexin-containing neurons to the motor nuclei of the trigeminal nerve and hypoglossal nucleus, and mRNA for melanin-concentrating hormone receptor, another hypothalamic peptide associated with nutrition, is found in all rat oromotor nuclei, including the trigeminal motor nucleus.

Forebrain structures certainly have a direct influence on trigeminal motor neuron activity. Electrical stimulation of the frontal cortex or central nucleus of the amygdala can produce rhythmic jaw movements in a number of species, including rats. In addition, the relatively short onset latencies of EPSPs in jaw-opening motoneurons and IPSPs in jaw-opening motoneurons suggested a monosynaptic pathway [7]. One brief report described several straight corticotrigeminal fibers. However, the prevailing view is that rhythmic masticatory movements are organized in the reticular formation of the brainstem. The short latency responses observed in Mo5 neurons upon corti-

cal stimulation may result from descending cortical projections to Mo5 dendrites that extend into the lateral tegmental field. Most direct projections originate from the medulla oblongata and pons, with minor contributions from the midbrain [4,6].

Midbrain Pathways

Midbrain projections to Mo5 consist almost entirely of cells in the rostral continuation of ipsilateral Me5. The axon terminals of individual Me5 cells are located predominantly in the dorsolateral region of Mo5 and monosynaptically excite masticatory neurons in response to peripheral stimulation or muscle spindle, or periodontal ligament [5,6]. Recent studies tracking the trajectory of intracellularly loaded Me5 neurons have shown that muscle spindle afferents, most sensitive to muscle stretch, project ipsilaterally directly to trigeminal motoneurons. Muscle spindle afferents that signal muscle length can influence trigeminal motor neurons bilaterally through the supratrigeminal region. Glutamate, acting on the non-N-Methyl-D-Aspartic Acid (non-NMDA) receptor, can mediate transmission between Me5 and Mo5.

Other Mo5 projections to the midbrain include a projection from the Edinger-Westphal nucleus, identified immunohistochemically as containing substance P, and an indirect pathway from the red nucleus. The red nucleus may influence Mo5 through the juxtatrigeminal area, that part of the lateral reticular formation that is located between Pr5 and the ventrolateral part of Mo5. Transynaptic transmission of Pseudorabies Virus (PRV) also suggests that the red nucleus influences Mo5 motoneurons through multisynaptic pathways [7,8].

Pontine Projections

The projections of the Mo5 pons begin rostrally at the level of the decussation of the connecting arm, medial to the lateral lemniscus in the area corresponding to group A7. This projection is the major source of Norepinephrine (NE) to Mo5, although other noradrenergic sources of Mo5 include cells beneath the locus coeruleus (SubC). Noradrenergic pathways influence on both reflex and rhythmic activity of Mo5. The masseter reflex, induced by electrical stimulation of Me5, is enhanced either by systemic treatment with the catecholamine precursor L-Dihydroxyphenylalanine (L-DOPA) or by direct electrical stimulation of area A7 [3,7]. As with excitatory amino acids and serotonin (5-hydroxytryptamine, 5-HT), norepinephrine iontophoresis on anterior digastric motoneurons enhances the rhythmic responses evoked by cortical stimulation. Groups of pontine cells that project bilaterally to Mo5 include cells surrounding Mo5 in the supratrigeminal and intertrigeminal nuclei. This area receives numerous inputs that potentially influence Mo5 neurons, including projections from the red nucleus and the midline pons and medullary Reticular Formation (RF). These structures were also transsynaptically labeled by Pseudorabies Virus (PRV) after injection into the masseter muscles and with relatively long survival times, suggesting an indirect effect on Mo5 neurons [7,9].

The main nucleus of the trigeminal nerve, primarily the dorsomedial region, also projects bilaterally to Mo5. This part of Pr5 receives cutaneous afferent projections from the oral region and is part of the jaw opening reflex pathway. Some Pr5 cells contain GABA and can inhibit jaw-closing motoneurons during jaw opening [8]. Inhibition of masticatory motor neurons during jaw opening is also mediated by cells of the supratrigeminal region, which receive projections directly from the primary afferents of the trigeminal nerve and indirectly through Pr5.

Medullary Projections

Mo5 projections from the medulla are based on a cell distribution continuous with pontine cells. Clusters of small neurons in the Parvocellular (PCRt) and Intermediate zone (IRt) reticular formation project predominantly ipsilaterally to Mo5, whereas clusters of larger neurons more medially located in the reticular formation project bilaterally. At level 12, the medial distribution is predominantly contralateral in the reticular nucleus of the dorsal Medulla (MdD) and Ventral Medulla (MdV). Based on dual injections of various retrograde fluorescent tracers, a small number of lateral medullary cells of the Reticular Formation (RF) project bilaterally to Mo5. Double-label studies also demonstrated that a small number of cells in the reticular formation project to both Mo5 and 12, or to Mo5 and 7. Slightly more double-label cells were obtained using the combination of Mo5 and 7 compared to the number obtained when using Mo5 and 12 [10,11]. Neurons in the rostral lateral medullary reticular formation (PCRt and IRt) appear to play an important role in the generation and coordination of rhythmic oral signals, since infusion of muscimol into this area suppresses both anterior bigastric and lingual EMG -activity associated with licking.

Although most Mo5-targeting premotor neurons use excitatory and inhibitory amino acids, some cells in the PCRt and MdD that project to Mo5 are cholinergic, and a population of more medially located cells in the nucleus giant cell (Gi) has been immunohistochemically identified as containing methionine-enkephalin. Ultrastructural studies show that PCRt neurons form both symmetric (inhibitory) and asymmetric (excitatory) synapses on dendrites and soma in Mo5. In addition, the gaseous neuromodulator nitric oxide depolarizes Mo5 neurons, and NADPH-containing neurons in brain RFs may be a source of nitrergic contribution to Mo5 [4,11].

Fluorescently labeled gold or fluorescent dextran injections into additional Mo5-labeled neurons in the ventral medulla, including the caudal raphe and paragigantocellular nuclei. These neurons may control state-dependent atonia during sleep or involvement of the masticatory muscles during high respiratory activity. Cells of the spinal trigeminal complex (pars oralis, interpolaris and caudalis) project to Mo5. The projection is predominantly ipsilateral.

Differential Mo5 projections have been studied by injecting PRV into the jaw opener and jaw closure muscles and by injecting small volumes of conventional retrograde tracers directly into specific motor pools. Some differences were obvious. Mesencephalic 5, Medial Parabrachial Nucleus (MBN), supratrigeminal nucleus, and dorsal operculum of Pr5, oralis, and interpolar muscles all had more extensive projections to closer motoneurons in the dorsal division compared with opening motoneurons in the ventromedial division [12]. In contrast, the lateral Parabrachial nucleus (PB), ventrally located neurons in the sensory trigeminal complex, and neurons in the α division of Gi preferentially project to opening motor neurons in the ventromedial division.

Serotonergic Projections

Serotonergic Mo5 projections account for approximately 13% of all synapses within Mo5 and are predominantly axodendritic. In the midbrain and pons, retrograde labeling combined with immunohistochemistry identified the dorsal raphe as one of the 5-HT sources for Mo5; however, autoradiographic studies have identified the superior central suture (median su-

ture), rather than the dorsal suture, as the primary source of suture projections to Mo5. Further caudally in the brainstem, serotonergic neurons of the raphe magnus, raphe nucleus pallidum, and raphe nuclei macula project to Mo5, as do neurons of the paragigantocellular nucleus [11,13]. Electrical stimulation of the caudal raphe depolarizes Mo5 neurons, an action that is blocked by serotonin antagonists. The trigeminal motor nucleus, together with the facial and hypoglossal nuclei, exhibits particularly dense labeling of the 5-HT2A and 5-HT3 receptor subtypes.

Microiontophoretic application of 5-HT to masticatory or anterior digastric motor neurons did not lead to a change in firing frequency. Serotonin, however, enhanced the excitatory response of these motoneurons induced by glutamate iontophoresis in Me5, activation of jaw extension afferents, or electrical stimulation of Me5 [13]. Serotonin enhances both NMDA and non-NMDA-mediated responses in Mo5 neurons that are induced by electrical stimulation of Me5.

Serotonergic inputs are also involved in rhythmic jaw movements. 5-HT iontophoresis on trigeminal motoneurons increased the number of rhythmically occurring spikes evoked by cortical stimulation. Serotonin may also play an important role beyond simply changing the excitability of neuronal inputs. In a tissue section preparation, Mo5 neurons showed bursting upon application of serotonin, suggesting that intrinsic properties of motor neuron membranes contribute to the formation of rhythmic chewing movements.

Amino Acid Neurotransmitters

Ultrastructural studies combined with immunohistochemistry have identified GABAergic, glycinergic, and glutaminergic synapses in the trigeminal motor nucleus. All three neurotransmitters formed both axosomatic and axodendritic synaptic terminals. In addition to labeled boutons containing exclusively GABA (22%) and glycine (32%), glycine and GABA coexisted in 46% of labeled boutons. Similar results were obtained by ultrastructural analysis of intracellularly filled and identified masticatory motoneurons. However, the proportion of coextensive GABA/glycine terminals was slightly lower [12]. Axoaxonal synapses were detected in Mo5, with GABA localized presynaptically in glutamate-labeled axons. Glutamate receptors on trigeminal motor neurons have not been characterized in detail but include NMDA receptors.

GABAergic and glycinergic neurons with projections to Mo5 originate predominantly from area h (mainly supratrigeminal and area medial to Mo5) and from PCRt. A smaller number of such cells are derived from the raphe nuclei magnus and the sensory trigeminal complex (Pr5 and interpolar muscle). There is significant overlap in the regional distribution of glutamatergic Mo5 projections with GABAergic and glycinergic projections originating from both area h and PCRt. A large body of literature indicates the involvement of excitatory and inhibitory amino acid neurotransmitters in the generation of rhythmic chewing activity evoked by cortical stimulation, as well as natural completed behavior. Inactivation of amino acid receptors in the medullary reticular formation modulates and suppresses food intake and rejection in awake rats [8,12].

Facial Nucleus

Internal Organization

Myotopic Organization

The cells within 7 are divided into several subdivisions, consisting primarily of cell groups separated by white matter but not by obvious cytoarchitectonic differences. Lateral, dorsolateral, intermediate, and medial subdivisions are readily visible in most Nissl-stained coronal sections. These divisions are evident from the rostro-caudal length of the nucleus; however, the medial division does not extend as far caudally as the intermediate and lateral divisions, and the dorsolateral division does not extend as far rostrally. In some sections, a ventromedial cluster of cells is visible, distinct from both the intermediate and medial sections, and in other sections, a dorsal "cap" can also be identified above the intermediate and medial sections [1]. Divisions designated in the atlas [Int. -2.3 mm] correspond to both the neuronal aggregates observed in Nissl-stained sections and the myotopic representations obtained from experimental studies.

Organization 7 was represented as a map to represent the branches of the facial nerve within the nucleus and to represent individual muscles. The minor discrepancies between these studies may be explained by multiple innervations of one muscle by different nerve branches and innervation of several muscles by a single nerve branch. However, several species exhibit a general pattern of organization in which the dorsal muscles are represented dorsally, the ventral muscles ventrally, and the anteroposterior axis lateromedial. The motor neurons innervating the nose are located laterally within 7, the perioral and orbital motor neurons are intermediate, and the facial motor neurons innervating the ear and neck are medial [8].

Detailed descriptions of the myotopic organization of individual pinna muscles indicate that, despite significant overlap within the medial compartment, motor neurons innervating the interscapularis and levator auricularis posterior muscles are squeezed between motor neurons innervating the transversus auricularis ventromedially and motor neurons innervating the anterior auricularis muscle dorsally. In the lateral division, the motor neurons that innervate the intrinsic muscles of the vibrissae, located dorsally, are located laterally than those that innervate the vibrissae, located more ventrally [1,14]. The anteroposterior position of individual vibrissae is not myotopically organized within 7. The motoneurons of the orbicularis oculi muscle have also been studied in some detail. Approximately 257 motoneurons per eyelid are distributed in the dorsal "cap" encompassing the mediolateral portion of 7. Like other motor nuclei, 7 is cholinergic; however, CGRP and urotensin II are also present in approximately 7 cells, as are CCK and urocortin mRNA.

Other muscles innervated by the facial nerve include the posterior digastric, styloid, and stapedius muscles and are innervated by motoneurons outside the main motor nucleus. Motor neurons innervating both the posterior belly of the digastric muscle and the stylohyoid muscle (active primarily during jaw opening) are located dorsal to the anterior pole of the 7th section along the exiting facial root and form the Accessory facial nucleus (Acs7). Within Acs7, motoneurons innervating the stylohyoid muscle are located ventral to those innervating the posterior belly of the digastric muscle. The size and shape of Acs7 cells are similar to those of 7, although there is a tendency for cell bodies and dendrites to elongate dorsoventrally. The axonal trajectory of Acs7 neurons is similar to that of other facial motoneurons, but the axons form a separate bundle parallel to the main exiting root. The location of Acs7, dorsal to the rostral end of 7, makes these cells almost adjacent to the trigeminal motoneurons innervating the anterior belly of the

digastric, with which they share both morphological and functional characteristics. The facial motor neurons innervating the stapedius muscle of the middle ear have not been studied in the rat, but in the cat they are located anteriorly 7, next to the superior olive [15].

Cytoarchitectonics and Dendritic Architecture

Neurons within 7 are stellate in shape and range in diameter from 15 to 55 µm. Estimates of the number of cells in 7 range from 3400 to 5800, with lower estimates including a correction factor for cell splitting. The dendritic arborization of individual HRP-filled neurons located in the medial, intermediate, and lateral divisions has been studied in sufficient detail. Primary dendrites extend in all directions, but the overall dendritic field remains within the subdivision, branching predominantly in a rostrocaudal direction. However, the dendritic fields of neurons in the lateral and intermediate divisions overlapped somewhat in the mediolateral direction, but the dendrites of neurons in the intermediate and medial divisions did not. Thus, within 7 itself, dendritic fields were functionally divided into those associated with orofacial function (intermediate and lateral divisions) and those innervating the auricular muscles (medial division) [1]. The overlap of dendritic fields between facial motoneurons from all subdivisions was more evident in RF dorsal to 7.

Unlike Mo5, there is no evidence for interneurons or axonal collaterals in 7. However, not all neurons in 7 innervate facial muscles. The small projection from 7 to the cerebellar flocculus does not originate from cells that project to the facial musculature, and several cells in 7 travels with the hypoglossal nerve to innervate the lingual musculature.

Afferent Projections

The various divisions of 7 receive significant and differentiated input from the nuclei of the midbrain, pons, and medulla oblongata. As with Mo5, rats do not appear to have forebrain projections to 7. In some cases, distinct central projections of 7 differentiate those divisions, which innervate the muscles of the orofacial region, and those that innervate the facial muscles of the ear and eye [16].

Midbrain Projections

In the midbrain, cells located anterior to the contralateral nucleus of the lateral lemniscus, i.e., the paralemniscal zone, project specifically to the medial division 7. Some of these projection neurons are either glycinergic or GABAergic. In cats, this area of the midbrain receives signals from the superior colliculus and is involved in orienting the pinna to sound.

Cells of the central gray, periocular nuclei (Edinger-Westphal nucleus, interstitial nucleus of Cajal and Darkshevich nucleus), olivary pretectal nucleus and reticular formation of the midbrain also project to 7 and provide a path for facial movements associated with emotional behavior (rage), eye reflexes (blinking) and vocal-facial behavior. Using rabies virus as a transneuronal tracer, Morcuende and colleagues elegantly demonstrated specific projections from the periolar nuclei, red nucleus, oculomotor nuclei, and deep cerebellar nuclei to orbicularis oculi motoneurons in dorsolateral division 7. Some parts of the midbrain pathway appear to be neurochemically specific. A subset of neurons in the central gray nucleus and Edinger-Westphal nucleus, retrogradely labeled by cholera toxin injections in 7, was immunocytochemically labeled with substance P [7]. Consistent with this observation, the greatest density of substance P immunoreactivity in 7 was concentrated over pools of motoneurons located in the intermediate and dorsal divisions that innervate the orbital muscles of the face. Retrogradely labeled cells in the olivary pretectal nucleus were immunocytochemically labeled with methionine-enkephalin, but the greatest Enkephalinergic (ENK) immunoreactivity in 7 was concentrated over facial motoneurons in the medial compartment innervating the ear [7,16].

The lateral and intermediate divisions of 7 receive projections from the contralateral red nucleus and provide relay of cortical and cerebellar inputs to 7. Electrical stimulation of the red nucleus caused movement of both whiskers and eyelids.

Pontine Paths

Differential projections onto the 7 units are clearly visible from the bridge. More cells in the ipsilateral Kolliker-Fuse (KF), supratrigeminal, and Parabrachial (PB) nuclei project to the lateral and intermediate divisions 7 than to the medial division. Area PB receives second-order vagal information and may be involved in exploratory sniffing, nasal breathing, and whisker movements, activities that require coordination between respiratory and facial motoneurons. Likewise, PB receives second-order taste information and can mediate taste-evoked facial responses. [17]. Projections from Pr5 to 7 are relatively rare and are limited mainly to the lateral regions. More cells in the reticular formation dorsal to the superior olive at the level of Mo5 project to the medial section out of 7 than to the lateral section.

Projections from the supratrigeminal area may serve as interneurons to mediate trigeminal reflex inhibition of intermedius 7 motoneurons. Similarly, neurons in both the supratrigeminal area and the PB may serve as interneurons for the basal ganglia's control of orofacial movements through projections from the entopeduncular nucleus [7,17]. Catecholaminergic projections to 7 from KF, the nucleus under the locus coeruleus (subcoeruleus) and area A5 project to all divisions of 7.

Medullary Projections

In the medulla, most projections to 7 come from cells of the reticular formation, distributed bilaterally in the PCRt and IRt at level 7, and MdD and MdV further caudally. However, a recent study using a more sensitive retrograde tracer cholera toxin identified additional populations of prefacial neurons in more medial, such as the nucleus gigantocellular, regions of the medullary reticular formation. Double labeling experiments with injections into both 7 and 12 or 7 and Mo5 established that up to 10% of labeled cells project to both motor nuclei. A slightly higher percentage of labeled neurons (15%) projected bilaterally to 7 [5,16]. Many of these cells are either GABAergic or glycinergic. Ultrastructural studies support a monosynaptic connection between medullary RF and 7 and indicate the presence of both symmetric and asymmetric synapses.

Different regions of the medullary RF project to different divisions, 7 although these differences are not as pronounced as the projections from the midbrain and pons. At level 12, many reticular neurons distributed bilaterally in the MdD, MdV and along the medial border of the ipsilateral Sp5C project to the intermediate and lateral divisions of 7. Cells of the caudal medulla projecting into the medial division of 7 tend to be located ventrally, i.e. dorsal to the lateral reticular nucleus and medial to Sp5C, and include cells in and around the nucleus ambiguus. Reticular neurons, which project predominantly to the medial part 7, extend to the cervical levels of the spinal cord, originating in

the intermediolateral gray column and the lateral part of the ventral horn. Disynaptic spinofacial reflexes may be mediated in part by spinofacial projection neurons that receive primary afferent terminals through dendrites that extend into spinal lamina IV. Some projections reach the facial nucleus from the ventral medulla oblongata and may be associated with respiratory activity or dyspnea [17].

Other medullary projections to 7 originate from the sensory trigeminal complex. The most complete description of these pathways used both anterograde and retrograde tracers and then tested for up to 12 collateral projections using dual tracers. All divisions of the sensory complex projected to 7, but there were significant differences in the nature of the projections [7]. Neurons of the spinal trigeminal complex were located throughout the nucleus but were predominantly clustered in the dorsal part of 5Sp. The projections were densest in the lateral divisions 7 and systematically decreased medially. The projection from principal 5 came almost exclusively from neurons in the ventral part of the nucleus.

These trigeminofacial and spinal dorsal horn projections appear to be topographically organized such that facial motoneurons receive cutaneous signals from areas overlying the muscles they innervate. Thus, projections from the mandibular branch of 5 to the dorsal region of 5Sp may influence vibrissae motoneurons located intermediate and laterally in 7. Likewise, periocular afferents that terminate in the ventral part of 5P project to orbicularis oculi motoneurons distributed dorsally within 7, mediating disynaptic blink reflex.

Minor projections to 7 include projections to medial division 7 from cells of the medial vestibular nuclei and projections from the nucleus of the tract solitary (sol) to the intermediate division.

Cholinergic and Peptidergic Pathways

Cholinergic terminals in 7 were characterized ultrastructurally. One source of this cholinergic input is the MdD cells, lateral to 12 and ventral to sol. Projections of substance P to the intermediate and dorsolateral divisions 7 also originate from this area of the reticular formation.

Other sources of substance P projections to 7 include the ventrolateral reticular formation of the medulla and the pallid and dark raphe nuclei. Neurons in these regions, identified immunohistochemically as containing both substance P and 5-HT, project predominantly to ventral regions 7 [16].

The ventrolateral reticular formation of the medullary medulla is also the source of ENK projections to 7, primarily to the medial division. As with substance P, enkephalinergic projection neurons 7 from the dark raphe nucleus and globus pallidus also contained 5-HT.

Serotonergic Pathways

Serotonergic fibers have been identified in 7 and appear either throughout 7 or are concentrated in the ventrolateral region. The sources of serotonergic projections appear to be the dark, large nuclei of the raphe and globus pallidus and form both axosomatic and axodendritic synapses. Iontophoretic application of 5-HT does not directly activate facial motor neurons, but it does alleviate excitatory responses elicited by other means. In vivo studies indicate that this facilitation is postsynaptic and mediated by the 5-HT2 and 5-HT1C receptor subtypes.

Hypoglossus Nucleus

Internal Organization

Myotopic Organization

The tongue consists of both external (genioglossus, GG; styloglossus, STY; hyoid, HY; palatoglossus, PG) and internal (vertical, V; transverse, T; superior longitudinal, SL; inferior longitudinal, IL) muscles. Although the Geniohyoid muscle (GH) is not a true lingual muscle, it shares embryological origins with the lingual muscles and often functions in conjunction with the GG, especially during tongue protrusion. [1]. The palatoglossus muscle (poorly expressed in rats) performs the function of the pharyngeal muscle.

The motor neurons innervating the lingual muscles originate from 12 and move along the hypoglossal nerve (12n). However, a small population of motoneurons within 7 exits the brainstem through 12n to innervate the lingual muscles. Several motoneurons from the ventral region of 12 move into the cervical muscle to innervate the motor fibers of the intrinsic and GH muscles.

The hypoglossal nucleus consists of dorsal and ventral divisions. The geniohyoid motoneurons form a separate cluster of neurons ventrolateral to the main nucleus. Axons arising from the dorsal division pass along the lateral branch of 12n and innervate the retractor lingual muscles. The axons of the ventral division, together with the axons of the GH, move along the medial branch to innervate the muscles that protrude the tongue [18]. In general, motoneurons innervating intrinsic muscles are located medial to those innervating extrinsic muscles.

Each styloid muscle is innervated by approximately 45 motoneurons located in the rostral third of the dorsal region. The hyoid muscle is innervated by approximately twice as many motoneurons in the dorsal division, caudal to the distribution of STY motoneurons. Intrinsic lingual motor neurons, which retract the tongue, are also located in the dorsal region. The hydrostatic model of lingual function predicts that contraction of the longitudinal muscles (inferior and superior) results in tongue shortening, and this prediction was confirmed directly by measuring retraction forces after microstimulation of individual longitudinal motor units. The upper and lower longitudinal motor neurons are located medial to the STY and HY motor neurons, with the lower longitudinal motor neurons located rostral to the upper longitudinal motor neurons. The number of intrinsic motor neurons greatly exceeds the number of extrinsic motor neurons, with longitudinal motor neurons making up about 75% of the neurons in the dorsal division [19].

The tongue protruding motor neurons are located in the ventral region, with the (extrinsic) motor neurons of the genioglossus muscle located lateral to the motor neurons innervating the intrinsic horizontal and vertical muscles. The ventral motor neurons innervating the intrinsic muscles are topographically represented such that the tip of the tongue is presented caudally within 12 and the base of the tongue is presented rostrally.

Immunohistological labeling (labeling) of various neurotransmitters, their precursors, derivatives or receptors is often demarcated or falls into myotopic subdivisions of 12. The distribution of catecholaminergic fibers, for example, determined by immunohistochemical labeling of Tyrosine Hydroxylase (TH), was evident in 12, but was particularly dense in the ventromedial quadrant of the caudal half of 12. In contrast, 5-HT immunoreactivity was particularly dense in both the dorsal portion of the

caudal two-thirds of 12 and in the ventrolateral region overlying GH motoneurons [1,19]. Although 5-HT1A and 5-HT1B receptor binding sites were particularly dense in the dorsal division of 12, consistent with the distribution of 5-HT immunoreactive terminals, similar binding sites were absent in the ventrolateral region of 12 (GH motor neurons), despite the presence of concentrations of immunoreactive terminals. Immunocytochemical labeling of the converting enzymes Dopamine β-Hydroxylase (DBH) and Phenylethanolamine (PNMT) was greatest in the ventromedial region of 12. This pattern of labeling confirmed the distribution of Catecholamine (CA) innervation observed previously and further implicated the NE as a major source. innervation of CA 12.

Ionotropic glutamate receptor subunits also showed some myotopic variation across 12. In particular, GluR1 (AMPA) was virtually absent in 12 motoneurons, except in cells located caudally. In contrast, other receptors AMPA (GluR2/3, GluR4), kainate (GluR5/6/7) and NMDA (NR1) were more evenly distributed across the 12 motoneurons. Presumptive interneurons in dorsolateral quadrant 12 stained well for GluR1. Physiological studies show that NMDA and non-NMDA receptors are colocalized within 12 [7].

Immunohistochemical labeling of adenosine deaminase was limited to dorsal 12. Adenosine may be involved in neurotransmission or other neuromodulatory actions. Adenosine labeling was transient in both 12 and (oro)facial motoneurons during development and disappeared by postnatal day 25. A possible correlation between temporal expression of adenosine and sucking behavior was noted by Senba and colleagues [20]. The enkephalinergic contribution to 12 was also differentially distributed. Immunohistochemically labeled ENK terminals were particularly dense in the ventrolateral portion, consistent with the location of GG motoneurons.

Cytoarchitectonics

Each half of the hypoglossal nucleus contains about 3,500 neurons. Most cells within 12 are motoneurons, but there is anatomical evidence for a small population of interneurons, confirming findings from earlier neurophysiological studies.

Motor Neurons

Cytoarchitectonic characteristics of dendritic size, shape, and orientation further differentiate motoneurons in different regions. 12 Dorsal cells appear fusiform, are oriented along the mediolateral axis, and range in diameter from 17 to 40 µm. Dorsal subdivision motoneurons innervating intrinsic muscles were significantly smaller (X = 25.7 µm) compared to extrinsic muscle motoneurons (X = 30.25 µm). Similarly, cells in the central region of the ventral division that innervate the intrinsic muscles were on average smaller (X = 23 µm) and more spherical in shape than the larger lateral multipolar motoneurons in the ventral division (X = 29.5 µm) [1,5]. Cell diameters (mean = 28.7 µm) were unimodally distributed in the ventrolateral compartment, leading Kitamura and colleagues to suggest the absence of γ-efferents, but subsequent studies clearly confirmed the earlier observation that both GH and longitudinal muscles have several muscle spindles.

Hypoglossal motoneurons are cholinergic and represent a subset of colocalized GABA. Peptides in 12 motor neurons include both galanin and CGRP, as well as urotensin II. Messenger RNA for both urocortin and CCK was also found in 12 motoneurons.

Interneurons

Interneurons in 12 were initially identified as cells not labeled after HRP was applied to the lingual muscles. These neurons were smaller (10–18 µm) than labeled motoneurons (25–50 µm), had fewer dendritic spines, and were restricted to the ventrolateral or dorsolateral borders of the nucleus. Data obtained from Golgi-impregnated neurons located in 12 and subsequently (re)sectioned for ultrastructural analysis confirmed that small neurons make synaptic contact within 12 [19]. An example obtained in a young rat demonstrated multiple axodendritic synapses between axons collateral to small interneuron, and hypoglossal motor neuron.

The GABAergic nature of interneurons is supported by both radioactive uptake studies and immunohistochemical staining of GABA and its synthetic enzyme, Glutamic Acid Decarboxylase (GAD). Immunocytochemical labeling of GABA and GAD fibers was clearly visible throughout 12, although staining was denser in the ventral regions of the nucleus, especially in the caudal half. Several positively stained GABAergic neurons were located laterally within 12 and along the dorsolateral border, i.e., in the same location as the HRP-identified interneurons. Neurons staining positive for GABA were small, 12–18 µm, round, and few in number. GABA inhibits 12 motor neurons. Interneurons in 12 may also have collaterals outside the nucleus. Injections of fluorescently labeled gold into the facial nucleus sequentially labeled several small neurons located laterally within 12 [19,20].

Dendritic Architecture

Neurons in 12 can be further classified based on dendritic morphology. Using Golgi-stained material, Ramon Y. Cajal designated sublingual cells as “external” when the dendrites extend beyond the nucleus and “internal” when the dendrites are confined to the nuclear region. Two particularly dense dendritic zones within 12 include the most dorsal part of the nucleus, immediately ventral to the dorsal motor nucleus of the vagus nerve (10), and the midline nucleus around the central canal. Some motoneuron dendrites extend into the contralateral nucleus. The dendritic orientation of cells labeled with either Golgi or cholera toxin HRP further allows for the discrimination of cells in different compartments. The dendrites of the cells of the dorsal region can be either internal or external. The external dendrites can reach 1 mm in length, extending laterally into the adjacent reticular formation (MdD and MdV) and in some cases reaching Sp5. Dendrites from these cells also extend into the ipsilateral SOL and very few cross 10 to reach the contralateral nucleus of the Solitary tract (SOL) [1]. The dendritic fields of cells in the ventral division include the apical dendrite, which branches within the dorsal divisions of 12, and the basal dendrites, which branch laterally within the 12 and adjacent reticular formation, extending ventrally into the Medial Longitudinal Fasciculus (MLF) and the dark raphe nuclei. The dendrites of multipolar cells in the center 12 branch throughout the nucleus. The dendrites of motoneurons within this compartment also form dendritic bundles in the rostral/caudal dimension and may provide a substrate for the simultaneous activation of synergistic motoneurons [1,5].

Afferent Projections

Afferent projections reach 12 from the cells of the midbrain, pons and medulla oblongata. Many of these projections originate from specific regions of the reticular formation responsible for the complex oromotor functions of chewing, licking, swal-

lowing, and breathing. Other RF projections control condition-dependent muscle tone of the tongue, and projections from the nucleus of the solitary tract and the sensory trigeminal complex mediate lingual reflexes.

Forebrain Pathways

Rats do not have direct cortical projections until 12. However, descending pathways activate the oromotor responses of chewing and licking, which are organized in the reticular formation of the brainstem. Damage to a small area of the anterolateral (orbital) cortex suppresses some tongue thrusting activity, but not the protrusion that occurs during rhythmic licking. Cortical areas that support microstimulation-induced ororhythmic responses send projections to widespread areas of the lateral medullary reticular formation and pontine reticular formation [1,21]. These brainstem regions overlap the location of neurons that rhythmically respond to licking or cortical microstimulation, as well as the location of neurons that project to 12. Descending projections from limbic structures to the midbrain provide additional pathways through which forebrain structures involved in feeding may ultimately affect 12 motor neurons.

Midbrain Projections

In the midbrain, several cells of the contralateral reticular formation project to 12, as shown by HRP. However, a similar study localized midbrain projections predominantly from within the central gray brain. There is some controversy as to whether Me5 projects directly to 12 via the Probst pathway. Although this projection was clearly visible using degeneration techniques, relatively few Me5 cells were labeled in retrograde HRP experiments. However, this projection may be directed to the dendrites of 12 motoneurons extending laterally into adjacent RFs and thus provide a substrate for proprioceptive interactions between the masseter and lingual muscles. Proprioceptive information from the jaw muscles can also reach 12 through the supratrigeminal region of the pons. This area receives a monosynaptic signal from Me5 and projects to 12 [7].

Pontine Projections

Several distributions of neurons near Mo5 reach 12. These include the ventral PB and intertrigeminal nuclei (bilateral), KF (ipsilateral), and the supratrigeminal area KF, part of the lateral tegmental group of catecholamine-containing cells, may be the source of NE projections to 12. Another source of pontine CA predictions up to 12 is SubC. Injections of HRP into 12 labeled scattered cells ventral to the locus coeruleus and medial to Mo5 in SubC and injections of tritiated amino acids in SubC induced reciprocal anterograde labeling within 12. Projections from the supratrigeminal area were prominent in the dorsal subdivision of 12 [1,17]. A subpopulation of supratrigeminal neurons stained for GABA or glycine, as do other projection neurons in up to 12 of the groups of neurons near Mo5.

The predominantly ipsilateral projection of Pr5 reaches 12 due to the distribution of relatively large cells (30–50 µm) located dorsomedially in the caudal two-thirds of the nucleus. Pr5 is topographically organized such that somatosensory afferent axons from the tongue project to the dorsomedial region. Thus, somatosensory information from the tongue can influence hypoglossal motoneurons through disynaptic pathways. Similarly, descending cortical fibers from the facial somatosensory cortex may influence lingual motoneurons via Pr5 [20].

Medullary Projections

Reticular formation. Most cells projecting to 12 are derived from the medullary RF. The central nucleus of the medullary brainstem, covering most of the Gi, is not involved in these direct projections; however, there are direct projections from the median raphe and the ventral divisions of the gigantocellular and paragiant cell nuclei.

Dorsal Medulla

In the dorsal medulla, reticular neurons projecting to 12 form a continuous column along the rostrocaudal axis. At the spinomedullary junction, projection cells are located bilaterally lateral to 12 in MdD and MdV (smaller). Rostral to 12, these cells are distributed bilaterally in the IRT and, to a lesser extent, in the PCRt. It is unclear whether there is spatial segregation of reticular neurons projecting to different lingual motoneurons. Neurons projecting to lingual retractor motoneurons have been described as dorsal to those projecting to the protrusions, or ventral.

Some reticular formation neurons project to more than one oromotor nucleus, and some RF interneurons project to multiple pools of 12 motoneurons. In double-labeling studies with injections of retrograde fluorescent markers in combinations of 12, Mo5, and 7, approximately 5–6% of labeled RF neurons scattered throughout single-projection cells were double-labeled. Medullary RF is a likely source of cholinergic effects on 12. Medullary RF cells projecting to 12 also stain positive for GABA and glycine [5,20].

Dorsal medullary RF projections to 12 are likely involved in the lingual component of completed behavior. Neurons located lateral to neuron 12 are active during both licking and swallowing, and the region located inferior to the caudal SOL is part of the central pattern generator for swallowing. Projection neurons located more rostrally in the medulla oblongata in the IRT are also active during licking, and administration of muscimol to this region suppresses this behavior.

Ventral Medulla

Ventral RF neurons form a critical substrate for respiratory rhythmogenesis, and direct projections to 12 have been demonstrated in both rats and cats [16]. In rats, neurons active during both inspiration and expiration were found quite far rostral in the ventrolateral medulla, just caudal to the facial nucleus, and appeared to overlap with the rostral ventrolateral reticular formation. In cats, some neurons in the ventral medulla project to both the phrenic nucleus and 12.

Neurons in the paragigantocellular and ventral giant cell nuclei also project to 12. These neurons were not well labeled using HRP, but were somewhat more prominent using fluorescently labeled gold, fast blue, or cholera toxin. Neurons in this area control muscle atonia during sleep. Stimulation of ventral and medial RF regions, including the ventral gigantocellular and paragigantocellular nuclei, decreased muscle tone in the neck muscles, and stimulation of this region was recently reported to release the inhibitory neurotransmitter, glycine, in 12.

However, other reports of electrical stimulation of the nucleus giant cell in areas that appear to overlap with the previous study suggest a predominant excitatory effect on hypoglossal motoneurons [1,20].

Raphe Nuclei

Neurons of the caudal raphe (dark, large and pallid) project to 12. Many projection neurons, mainly from the dark and pallid nuclei, stained for 5-HT and serotonergic terminals in 12, have been identified ultrastructurally. A number of 5-HT projection neurons also contained substance P; a smaller amount contained enkephalin.

The physiological effects of 5-HT on 12 motor neurons are complex. Microinjection of 5-HT directly into 12 motor neurons increased activity levels, and microdialysis delivery of 5-HT increased GG activity in awake rats during sleep-wake cycles [7]. On the other hand, sublingual motoneurons were suppressed by infusion of 5-HT in the tissue slice preparation, and there was also a decrease in the response to electrical or chemical stimulation of the suture. It has been suggested that serotonin may depolarize hypoglossal motoneurons postsynaptically but inhibit excitatory glutamatergic input presynaptically. Because raphe neurons are more active in the waking state, glutamatergic inputs, possibly related to respiration, may be selectively suppressed and allow raphe neurons to enhance hyoid muscle function associated with other oromotor functions such as feeding. Binding sites for 5-HT1A and 5-HT1B receptors are widespread in the hypoglossal nucleus but rare in the ventrolateral nucleus, which contains the geniohyoid motoneurons. Messenger RNA for 5-HT1B, 5-HT2A, and 5-HT2B receptors was detected in 12, but no mRNA for 5-HT1A was detected [1,14].

Input of the Trigeminal and Solitary Nuclei

The second bilateral distribution of medullary cells projecting to 12 originates from the spinal trigeminal complex. Projection neurons are clustered predominantly in the dorsal part of Sp5, the region that receives the bulk of trigeminal afferents from the tongue, although some projection neurons are scattered throughout the nuclei. Similarly, small injections of anterograde tracers into Sp5C labeled both dorsal and ventral divisions 12. In the cat, these neurons are associated with the polysynaptic trigeminolingual reflex evoked by electrical stimulation of the trigeminal nerve. Multiple pathways from Sp5 to 12 include projections through short axonal interneurons into adjacent RFs and extensions of hypoglossal motor neuron dendrites into this area [20]. A more recent study using anterograde tracers injected into Sp5 demonstrated that the majority of RF projections terminated in the PCRt and MdD, a smaller number in the IRt and MdV, and the fewest in Gi. Cortical projections from Sp5 have also been proposed as part of the corticohyoid pathway in cats. Inhibitory interneurons adjacent to 12 are also involved in the trigeminohyohyoid reflexes.

Relatively few cells from the SOL project to 12. Those that do are ipsilateral and located predominantly in the caudal half of the nucleus in an area that receives afferents through the glossopharyngeal and vagus nerves. Sublingual reflexes induced by stimulation of these nerves may be mediated by interneurons in the SOL or by direct synaptic contact through sublingual dendrites that extend into the SOL [1,5].

Neuropeptide Input

Synaptic terminals within 12 containing substance P and enkephalins have been described in studies combining immunohistochemistry and electron microscopy. Substance P terminals appeared to be distributed among 12; however, ENK terminals were densest in the ventral division 12, especially at the rostral levels that include the GG muscles. ENK endings were predominantly axodendritic; however, the endings of substance P can be either axosomatic or axodendritic. In the rat, substance P terminals appear to be located on interneurons, but in cats there is clear anatomical and physiological evidence that substance P terminals are located directly on the soma and dendrites of motoneurons. The main source of substance P is probably the caudal suture. Substance P and enkephalin colocalize in different populations of 5-HT-containing cells of the caudal raphe; however, this represents a relatively rare ENK projection [7,20].

Other sources of ENK input to 12 may be the medullary RF, SOL or PB, the spinal trigeminal complex, or areas involved in respiratory function projecting to 12, including the KF and ventrolateral medullary RF. Another peptide presents in 12 is Thyrotropin Releasing Hormone (TRH). In a tissue slice preparation, TRH depolarized 12 neurons, increased spontaneous activity, and enhanced responses evoked by NMDA iontophoresis.

Lingual Proprioceptors

Another set of afferent projections to 12 is proprioceptive. Approximately six muscle spindles were consistently observed in the GH muscles and a smaller but more variable number in the longitudinal, HY, and GG muscles. No muscle spindles were observed in other extrinsic or intrinsic muscles. These muscle spindles, although few in number, are proportional to those found in primates when expressed as the ratio of number of spindles to muscle volume [15]. Own afferent fibers of proprioceptors of muscles with cell bodies in spinal C2 and C3 pass into the cervical cavity; cells from extrinsic muscles (including GH) have their cell bodies in the jugulonodose or trigeminal ganglion and move from 12n. Fibers going to 12n, with cell bodies located in the trigeminal or jugulonodose ganglia, terminate at Sp5i and Sp5c. In addition, 12n axons with cell bodies in the trigeminal ganglion also terminate in Pr5, in contrast to the central end of jugulonodose ganglion cells, which terminate in the caudal SOL. Spinal afferents from the tongue end in the I and V laminae of the posterior cervical horn. In all cases, the terminal endings were not expressed within 12, indicating the absence of monosynaptic contacts. Lingual proprioceptive activity also influences other associated oral motor nuclei, and electrical stimulation of 12n produces responses in both facial and trigeminal motoneurons [1].

These projections do not provide a complete description of all direct influences on hypoglossal motoneurons. The extensive dendritic ramifications of 12 motoneurons throughout the adjacent RF, raphe major nucleus, and MLF make further monosynaptic influence from other CNS regions inevitable [18]. Cerebellar influences on 12, for example, may be mediated by 12 motoneuron dendrites in the MLF. Projections to the hypoglossal nerve dendrites extending into the RF may also mediate sensory information to 12 from visual, somatosensory, and vestibular sources.

Conclusions

Each of the orofacial motor nuclei is organized into several divisions, defined both myotopically and cytoarchitectonically. In the case of Mo5 and 12, the muscle antagonists are divided into separate divisions in which the motor agonists have adjacent representation. In 7, pronounced topography associated with peripheral muscles is evident. Myotopic subdivisions are further determined by the specific central projections they receive. The mesencephalic area 5 and supratrigeminal area predominantly project toward adjacent motoneurons in Mo5; the

lateral PB and Gi project predominantly over the jaw-opening motor neurons. Within 7, motoneurons of the medial auricular musculature receive highly specific projections from the paralemniscal area of the midbrain and ENK projections from the olivary pretectal nucleus. These projections contrast with those of the orally related intermediate and lateral divisions 7 of the KF and the ventral PB in the pons and MdD in the medulla.

Although these central projections serve to differentiate the subdivisions of the motor nuclei, there is also compelling evidence of overlapping central projections of the oromotor nuclei, which unites them functionally. Neurons in the PCRt and IRt rostrally, in the MdD and MdV caudally, and in the ventral medulla have extensive projections to the oromotor nuclei, and double-label studies reveal single neurons in these fields with multiple projections. Although such projections undoubtedly serve as outputs of the central generators of patterns of chewing, swallowing and breathing, the systems controlling the oromotor nuclei can more accurately be characterized as interacting multifunctional systems. Such systems must not only act as pattern generators, for example, for coordination between the lingual and trigeminal motor neurons during mastication, but also must coordinate muscle participation between competing functions such as breathing and swallowing. The substrates appear to be multifunctional, since neurons involved in patterning one function, such as licking, may also be involved in another, such as swallowing. Following the progress made in invertebrate systems, the identification of neuromodulators in the afferent pathways driving oromotor neurons, as well as the motoneurons themselves, provides a future direction for the study of complex oromotor functions.

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