Abstract: Corticofugal projections to neurons in the medullary dorsal horn, i.e., the trigeminal spinal subnucleus caudalis (Sp5C), are thought to play a critical role in regulating nociceptive information processing in the trigeminal nervous system. The Sp5C consists of 5 layers, each of which exhibits its own characteristic features of cellular organization. Therefore, the layers receiving corticofugal projections must be identified when discussing the role of the cerebral cortex in nociception arising from the trigeminal nerve. It is also necessary to discriminate between layers of the Sp5C where corticofugal projections terminate, because the Sp5C involves glutamatergic neurons and GABAergic/glycinergic neurons, which correspond to excitatory and inhibitory neurons, respectively. This review summarizes descending projections from the cerebral cortex, including the primary and secondary somatosensory and insular cortices, to the Sp5C.

Keywords: corticofugal, insular cortex, pain, somatosensory cortex, trigeminal spinal nucleus caudalis

Introduction

Primary sensory neurons, whose somata are located in the trigeminal ganglion, convey somatosensory information from orofacial structures such as the dental pulp, periodontal ligament, oral mucosa, and facial skin. Regardless of the sensory modality of these primary sensory neurons, i.e., tactile sensation, thermal sensation, or nociception, these primary sensory neurons project to the trigeminal complex, including the trigeminal nucleus principalis and the spinal subnucleus oralis (Sp5O), interpolaris (Sp5I), and caudalis (Sp5C) [1].

Among these trigeminal sensory nuclei, Sp5C neurons principally process nociceptive information [2]. The Sp5C, which is also called the medullary dorsal horn [3-5], is located in the most caudal part of the medulla oblongata. The somatotopic organization of facial and oral structures in the Sp5C was clearly described by Shigenaga et al. [6]: the midline of oral structures and the most anterior part of the face are represented in the most rostral part of the Sp5C, whereas lateral/posterior parts of the face are represented in the caudal Sp5C (onionskin representation). In addition to the rostrocaudal representation of orofacial structures in the Sp5C, the dorsoventral and mediolateral representation of Sp5C is also well documented: intraoral and facial structures are represented in the dorsomedial and ventrolateral parts of the Sp5C, respectively [7,8].

This review focuses on the functional roles of the cerebral cortex in the neural activities of the Sp5C.

Layer organization of the Sp5C

The Sp5C is a continuous structure that extends from the level slightly rostral to the obex to the spinal cord and has a similar layer arrangement to that of the cervical dorsal horn. Among the primary afferents of the trigeminal nerve, Aδ-fibers, which are lightly myelinated, and C-fibers, which are unmyelinated and substance P-immunopositive, are thought to carry nociceptive information. Among these nociceptive fibers, Aδ-fibers project mainly to laminae I and V (reticular formation medially adjacent to lamina IV) and slightly to outer II (IIO) [9,10], while C-fibers project to laminae I and IIO and slightly to inner II (III) [11]. Mizuno and colleagues demonstrated the existence of substance P receptors in the postsynaptic neurons of laminae I and II [12,13]. In contrast, heavily myelinated Aβ-fibers project to laminae V, as well as to the magnocellular layers (laminae III and IV), in which large multipolar cells are involved, and to other small and medium-sized cells [10,14]. Renihan et al. reported that neurons activated by vibrissa and/or guard hair deflection are located in layers III, IV, and superficial V [15].

Here, the layer structure of laminae I and II of the Sp5C, which principally receive corticofugal descending projections, is described.

Lamina I of the Sp5C

Lamina I corresponds to the marginal layer, described by Olszewski [1], that is located in the most superficial layer of the Sp5C. Many studies have reported that lamina I neurons send their axons to higher-order brain regions, including the thalamus, hypothalamus, and parabrachial nucleus [16-20]. Together with the distribution patterns of nociceptive fibers described above, neurons in lamina I are critical in relaying nociceptive information from the peripheral nervous system to higher-order brain regions.

Lamina I neurons in the cat have been classified into 4 subtypes by Golgi staining as spiny and smooth pyramidal cells and compact and loose multipolar neurons [3]. A similar study was performed in lamina I of the cervical spinal cord of the rat, in which lamina I neurons were classified as (1) fusiform spiny cells with longitudinal and spindle-shaped perikarya, (2) multipolar cells with dense dendritic arbors, (3) aspiny cells with polygonal cell bodies flattened in the horizontal plane and horizontal dendritic arbors confined to lamina I, and (4) pyramidal cells with longitudinally elongated perikarya [21]. Li et al. (2000) divided the projection neurons into 2 subtypes, according to axonal branching patterns: neurons with rare axon collaterals within the Sp5C and those with axon collaterals in laminae I, II, and III [22]. They also reported that half these projection neurons had neurokinin-1 receptor-immunopositive perikarya (see also [23]), suggesting that they convey nociceptive information [22].

In addition to the projection neurons, there are interneurons, some of which are GABAergic and glycinergic [24-26]. These inhibitory Sp5C neurons receive substance P-immunopositive primary fiber projections, which suggests that nociceptive information is directly carried by not only excitatory but also inhibitory neurons in lamina I of the Sp5C [13].

Lamina II of the Sp5C

Lamina II is the deeper layer adjacent to lamina I and is often called the substantia gelatinosa (lamina II), as described by Olszewski [1], because it has a translucent appearance attributable to the low concentration of myelinated fibers [4]. Lamina II is further divided into IIO and II, which are believed to have different roles in somatosensory information processing. Nociceptive Aδ-fibers terminate in IIO only, while nociceptive C-fibers terminate in laminae IIO and IIII [27]. Neurokinin-1-immunopositive neurons are present in laminae I and IIIO [23].

A morphological study using Golgi staining reported 4 interneuron subtypes in lamina II: (1) spiny stalked cells mainly located in lamina IIO, with cone-shaped dendrites extending medially across laminae II-II and extensive canopy-like axons in lamina I, (2) clustered islet cells...
whose dendrites and axons are largely confined to layer II, (3) arboreal cells whose dendrites are tree-like and mostly confined to lamina II, and (4) II-III border cells with extensive rostral and caudal dendrites, mostly in laminae II and III, with a few branches extending into lamina I [4]. The axons of these interneurons arborize in laminae II and III, and a few collaterals extend into lamina I. Similar to lamina I, lamina II contains GABAergic/glycinergic interneurons [24-26], and the latter 3 cell subtypes (islet, arboreal, and II-III border cells) are considered inhibitory interneurons [4]. Indeed, Wang et al. demonstrated GABAergic and glycinergic neurons in lamina II [13].

Li et al. classified lamina II neurons into 3 subtypes in relation to the pattern of axonal arborization [28]. Projection neurons are characterized by their axons, which principally project to the rostral or caudal laminae I and III of the Sp5C, Sp5I, and cervical dorsal horn, and their spiny dendrites that spread through all the laminae of the Sp5C. In contrast, the interneurons are classified into 2 subtypes. One subtype consists of interneurons with dense axonal arborizations that have elongated and oval patterns and are located principally in lamina II. Their dendrites arise from the rostral and caudal pole of the cell bodies and mainly extended rostrally and caudally, parallel to the rostrocaudal axis of lamina II, and exhibit an arborized pattern similar to that of their axons. The other interneurons, whose somata are small and round, have sparse axonal arborization that spreads radially to all laminae of the Sp5C.

Cerebrocortical areas that process oral sensations

Somatosensation mediated via oral structures is processed in the cerebral cortex, including the primary (S1) and secondary somatosensory (S2) and insular cortices (IC). Electrical stimulation of the dental pulp principally activates the border between S2 and IC caudally adjacent to the middle cerebral artery, named S2/IOR [29-35]. In contrast to S2/IOR activation, S1 exhibits less activation by dental pulp stimulation, which is also true for electrical stimulation of the periodontal ligament [36,37]. It is worth noting that mechanical stimulation of the periodontal ligament, by pulling the maxillary first molar, induces greater S1 activation than S2/IOR activation [38,39]. These findings suggest that S1 and S2/IOR have different roles in somatosensory information processing, namely, that non-nociceptive and nociceptive information is principally processed in S1 and S2/IOR, respectively.

Anatomy of descending projections from the somatosensory cortex to the Sp5C

The trigeminal complex receives descending projections from various sensory cortical regions, including the somatosensory, primary auditory, and primary visual cortices [40-51]. In addition to these sensory cortices, other cortical regions, such as the motor and peduncular cortical neurons, also send their axons to the Sp5C [45,52]. Among these cortices, S1, S2, and IC are the main cortical regions that project to the Sp5C [47]. Corticofugal projections to the brainstem, including the trigeminal complex, have been examined, especially focusing on S1 and S2. Projection neurons from the S1/S2—trigeminal complex, including the Sp5C, are pyramidal neurons located in layers V and V1 in rats [40,46,53] and cats [43]. Among these infragranular pyramidal neurons, the largest pyramidal neurons in the deep layer V (Vb) are the principal neurons projecting to the trigeminal complex in rats [46,53,54].

S1/S2 neurons bilaterally project to the trigeminal complex, with a contralateral dominance in adult animals [43,41,48-50]. In kittens, bilateral corticofugal projection from the somatosensory cortex to the Sp5C appears 1 week after birth, and by postnatal week 4 the descending projection pattern shifts from bilateral to contralateral dominance by elimination of ipsilateral projections [44]. Somatotopic organization in S1 and S2 is well documented [30,55]. According to the somatotopic map, the cortical region corresponding to oral structures [41] is located in the most ventral part of S1 and S2 [30,55]. Descending projections from the somatosensory cortex to the spinal cord and trigeminal complex show somatotopic organization: the hindlimb region in S1 projects to the spinal cord at the lumbar level, whereas the facial representation of S1 projects to the trigeminal complex [40].

Projections from the facial region in S1 to the Sp5C principally target the marginal zone (lamina I) and substantia gelatinosa (lamina II) [41,44,45,51] but also target laminae III-V [47,56]. In addition to the rostrocaudal somatotopic organization of the trigeminal complex, there is somatotopy in the Sp5C corresponding to the region in S1 [49]: regions in S1 responding to stimulation of the lingual nerve, mental nerve, infraorbital nerve, and frontal nerve are rostrocaudally arranged in S1, and each S1 region projects to the most medial superficial layer, medial deep layer, middle superficial and deep layer, and lateral deep layer in Sp5C, respectively. This corticofugal somatotopic organization in the Sp5C almost replicates the pattern of S2→Sp5C projections [48]. In other words, terminals of descending projections from S2 regions to the Sp5C corresponding to the branches of the trigeminal nerve mostly overlap those from S1 [54].

Function of projections from the somatosensory cortex to the Sp5C

The physiological function of the projections from the somatosensory cortex to the Sp5C has been explored in cats [5] and rats [51,56,57]. Sessle BJ et al. estimated the effect of electrical stimulation of the somatosensory cortex on nociception by conducting electromyogram recordings in the digastric muscle during tooth pulp or infraorbital nerve stimulation (jaw-opening reflex), combined with extracellular recordings in Sp5C neurons [5]. Electrical stimulation of the peri- and nucleus raphe magnum, both of which play a central role in the descending inhibition of pain [5,58,59], consistently suppressed the jaw-opening reflex, whereas stimulation of the somatosensory cortex suppressed the jaw-opening reflex in response to tooth pulp stimulation in 1 of 3 cats. Similarly, activity recorded from Sp5C neurons responding to tooth pulp stimulation was almost completely suppressed by stimulation of the peripheral gray matter or nucleus raphe magnum, whereas 48% of Sp5C neurons were suppressed by stimulation of the somatosensory cortex. Gujyo et al. demonstrated that stimulation of S2, but not S1, reduced c-Fos expression in response to formalin injection into the lower lip [56].

Descending projections from the insular cortex to the Sp5C

The IC is another cortical region that processes nociception, as described above. By retrograde and anterograde tracing in the rat, the principal cortical region that projects to the Sp5C was found to be S1 and the IC, whereas adjacent regions, such as the cuneate nucleus, receive corticofugal inputs from S1, S2, and M1, and the subnucleus reticularis dorsalis receives inputs from wider cortical regions, including S1, S2, M1, M2, and the IC [47]. The principal projection from the IC to Sp5C was supported by findings from a later anatomical study [50], which reported dense descending projections from the IC to Sp5C and spatial correspondence between the IC and Sp5C. The rostral and caudal IC projects mainly to the medial and lateral regions of the Sp5C, respectively. In terms of the layer specificity of descending projections from the IC to Sp5C, laminae II/II are dominant [47,50].

This anatomical evidence strongly suggests that the IC affects nociception in the trigeminal nervous system by regulating synaptic transmission, including projection neurons. However, the critical question is which neuronal subtype—excitatory glutamatergic neurons, including projection neurons, or GABAergic/glycinergic inhibitory neurons—receives IC→Sp5C projections. In addition, the physiological function of the IC→Sp5C projection remains unknown. These issues should be further examined in the near future.

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Conflict of interest

None declared.

References

1. Olszewski J (1950) On the anatomical and functional organization of the spinal trigeminal nucleus. J Comp Neurol 92, 401-413.

2. Sessle BJ (2000) Acute and chronic craniofacial pain: brainstem mechanisms of nocicep-
31. Nakamura H, Shirakawa T, Koshikawa N, Kobayashi M (2016) Distinct excitation to pulpal stimuli between somatosensory and insular cortices. J Dent Res 95, 180-187.
32. Yokota E, Kuyanagi Y, Nakamura H, Horinuki E, Oi Y, Kobayashi M (2016) Opposite effects of mu and delta opioid receptor agonists on excitatory propagation induced in rat somatosensory and insular cortices by dental pulp stimulation. Neuron Lett 628, 52-58.
33. Fujita S, Kaneo K, Nakamura H, Kobayashi M (2017) Spatiotemporal profiles of proprioception processed by the musketer muscle spindles in rat cerebral cortex: an optical imaging study. Front Neurol 8, 57.
34. Murayama S, Yamamoto K, Kaneo M, Ogiso B, Kobayashi M (2017) Ablation of C-fibers decreases quantal size of GABAergic synaptic transmission in the insular cortex. Neurosci Res 116, 170-179.
35. Fujita S, Yamamoto K, Kobayashi M (2019) Trigeminal nerve transection-induced neuropeptide changes in the somatosensory and insular cortices in a rat ectopic pain model. eNeuro 6, e0462-18.
36. Horinuki E, Shioda M, Shinizu K, Kobayashi N, Kobayashi M (2015) Orthodentic force facilitates cortical responses to periodontal stimulation. J Dent Res 94, 1158-1166.
37. Horinuki E, Yamamoto K, Shinizu N, Kobayashi K, Kobayashi M (2016) Sequential changes in cortical activity from periodontal to dental pulp stimulation. J Dent Res 95, 897-905.
38. Kaneo M, Horinuki E, Shinizu N, Kobayashi K (2017) Physiological profiles of cortical responses to mechanical stimulation of the tooth in the rat: an optical imaging study. J Dent Res 96, 158-164.
39. Kaneko J, Dohi H, Horiguchi K, Fujii K, Oshima M, Kayahara T (2018) Experimental tooth movement temporarily changes neural excitation and topographical map in rat somatosensory cortex. Brain Res 1698, 62-69.
40. Wise SP, Murphy EA, Couder JD (1979) Somatotopic organization of corticospinal and corticotomy neurons in the rat. Neuroscience 4, 65-78.
41. Dunn RCJ, Chong KL (1982) Sensorimotor cortical projections to the marginal zone of the trigeminal subnucleus caudalis. J Comp Neurol 213, 1-22.
42. Dunn RCJ, Tolbert DL (1982) The corticotegmental projection in the cat. A study of the organization of corticopetal projections to the spinal trigeminal nucleus. Brain Res 240, 13-25.
43. Tashiro T, Matsuyama T, Higo S (1983) Distribution of cells of origin of the corticospinal projections to the nucleus caudalis of the spinal trigeminal complex in the cat. A horseradish peroxidase (HRP) study. Exp Neurol 80, 178-185.
44. Tolbert DL, Dunn RCJ, Vogter GA (1984) The postnatal development of corticostriatal projections in the cat. J Comp Neurol 228, 478-490.
45. Newman DB, Hilleary SK, Ginsberg CY (1989) Nuclear terminations of corticospinal fiber systems in rats. Brain Behav Evol 34, 223-264.
46. Killinger HF, Kraka C, Klaue NL (1989) Laminar and areal differences in the origin of the subcortical projection neurons of the rat somatosensory cortex. J Comp Neurol 332, 482-445.
47. Desbois C, Le Bars D, Villanueva L (1999) Organization of cortical projections to the mediator subnucleus reticularis dorsalis: a retrograde and anterograde tracing study in the rat. J Comp Neurol 410, 170-196.
48. Haque T, Akhter F, Kato T, Sato F, Takeda R, Higashiyama K et al. (2012) Somatotopic direct projections from cerebral areas of somatosensory cortex to trigeminal sensory nuclear complex in rats. Neuroscience 219, 214-233.
49. Tomita A, Kato T, Sato F, Haque T, Oka A, Yamamoto M et al. (2012) Somatotopic direct projections from cerebral areas of primary somatosensory cortex to pons and medulla, especially to trigeminal sensory nuclear complex, in rats. Neuroscience 200, 166-185.
50. Sato F, Akhter F, Haque T, Kato T, Takeda R, Nagase Y et al. (2013) Projections from the insular cortex to pain-receptive trigeminal caudal subnucleus (medullary dorsal horn) and other lower brainstem areas in rats. Neuroscience 233, 9-27.
51. Castro A, Raver C, Li Y, Uddin O, Rubin D, Ji Y et al. (2017) Cortical regulation of nociception in the trigeminal nucleus caudalis. J Neurosci 37, 11431-11440.
52. Akhter F, Haque T, Sato F, Kato T, Ohara H, Fujita S et al. (2014) Projections from the dorsal peduncular cortex to the trigeminal subnucleus caudalis (medullary dorsal horn) and other lower brainstem areas in rats. Neuroscience 266, 25-37.
53. Wise SP, Jones EG (1977) Cells of origin and terminal distribution of descending projections of the rat somatosensory cortex. J Comp Neurol 175, 129-157.
54. Smith JB, Watson GD, Alloway KD, Schwarz C, Chakrabarti S (2015) Corticofugal projection patterns of whisker somatosensory cortex to the sensory trigeminal nucleus. Front Neural Circuits 9, 53.
55. Remple MS, Henry EC, Catania KC (2003) Organization of somatosensory cortex in the rodent brain. Brain Res 996, 213-229.
56. Akhter F, Haque T, Kato T, Sato F, Takeda R, Higashiyama K et al. (2012) Somatotopic direct projections from cerebral areas of somatosensory cortex to trigeminal sensory nuclear complex in rats. Neuroscience 219, 214-233.
57. Tomita A, Kato T, Sato F, Haque T, Oka A, Yamamoto M et al. (2012) Somatotopic direct projections from cerebral areas of primary somatosensory cortex to pons and medulla, especially to trigeminal sensory nuclear complex, in rats. Neuroscience 200, 166-185.
58. Sato F, Akhter F, Haque T, Kato T, Takeda R, Nagase Y et al. (2013) Projections from the insular cortex to pain-receptive trigeminal caudal subnucleus (medullary dorsal horn) and other lower brainstem areas in rats. Neuroscience 233, 9-27.
59. Castro A, Raver C, Li Y, Uddin O, Rubin D, Ji Y et al. (2017) Cortical regulation of nociception in the trigeminal nucleus caudalis. J Neurosci 37, 11431-11440.
60. Akhter F, Haque T, Sato F, Kato T, Ohara H, Fujita S et al. (2014) Projections from the dorsal peduncular cortex to the trigeminal subnucleus caudalis (medullary dorsal horn) and other lower brainstem areas in rats. Neuroscience 266, 25-37.
61. Wise SP, Jones EG (1977) Cells of origin and terminal distribution of descending projections of the rat somatosensory cortex. J Comp Neurol 175, 129-157.
62. Smith JB, Watson GD, Alloway KD, Schwarz C, Chakrabarti S (2015) Corticofugal projection patterns of whisker somatosensory cortex to the sensory trigeminal nucleus. Front Neural Circuits 9, 53.
63. Remple MS, Henry EC, Catania KC (2003) Organization of somatosensory cortex in the rodent brain. Brain Res 996, 213-229.