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Review

The interesting whisker/barrel system

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Abstract

Introduction

In the late 20th century, Woolsey and Van der Loos discovered a specific projection map in the rodent somatosensory cortex corresponding to the contralateral face whiskers, designated barrel. Because rodents are nocturnal animals, their whiskers serve to recognize the external world, similar to our eyes and fingers.

Each barrel is associated with an individual whisker on the snout, and ambient information received by the whiskers is conveyed to the somatosensory cortex via the trigeminal ganglia, trigeminal nuclei, and thalami. Because the brain maps for whiskers also exist above the brainstem, it suggested that one-barrel processes sensory information for one facial whisker. This one-to-one relationship, thought to be important in transmitting information correctly. Moreover, if sensory input is blocked from early development, the whisker-matched brain map will be unable to form, or the formed map will disappear. As such, the whisker/barrel system is refined during postnatal periods by neural activity elicited by stimuli to vibrissae. Studying the whisker/barrel system is advantageous, as it can be easily probed, with both anatomical and functional techniques, and for nearly half a century, many anatomists and electrophysiologists have elucidated the mechanisms in the whisker/barrel system, such as activity-dependent synaptogenesis of barrel cortex. This review outlines the detailed pathway, history, mechanism of development, as well as recent evidence of the whisker/barrel system from an anatomical perspective and is meant to spur the interest of young neuroanatomists in this elegant neural circuit.

Conclusion

Given the simple sensory pathway amenable to interrogation, the whisker/barrel system of rodents attracts researchers' attention as an important model for understanding basic principles of cerebral cortical development in mammals. Moreover, the visualisation of brain map facilitates further study of the whisker/barrel system. Therefore, we encourage investigators interested in the role of sensory experience on neuronal networks to study the whisker/barrel system.

Introduction

Cerebral sensory neurons have stimulus selectivity, allowing them to react to a specific range of stimuli from the external world, called the receptive field of the cell. In many cases, cells possessing similar properties (receptive field, stimulus selectivity) form modular structures in the brain. The arrangement of the modular structure conserves the topologic spatial relationship observed on the sensory epithelium of the sensory receptor that supplies ambient information. The representation of such information in the brain is called a projection map.

In 1970, Woolsey and Van der Loos found receptive fields in the somatosensory area of the mouse cortex that reacted to whisker stimulation[1]. They discovered 'barrels' that are independent cytoarchitectonic units in layer 4 (L4), which are circularly aligned cell populations in a projection map of the brain. Interestingly, the arrangement of barrels is the same as the pattern of whiskers on the mystacial pad. Thomas Woolsey's father, Clinton Woolsey, revealed the projection map responsive to vision, audition, and peripheral somatic sensation in various animals using surface evoked potential recording techniques[2,3]. Thomas helped his father, and himself reported brain maps in somatosensory, auditory, and visual area of the mouse using the same techniques4. Together, they formulated the hypothesis that one 'barrel' will correspond to one whisker. They verified their hypothesis by trimming whiskers of postnatal 0-day (P0) mice. It turned out that the barrel corresponding to the ablated whisker disappeared at P5. However, the barrel was unaffected by whisker trimming after P65. Around the same time, Killackey reported that ventral posteromedial (VPM) nucleus neurons in the thalamus project to the barrel cortex and the pathway is the main trajectory of rodents in higher animals[6].

By recording activity of neurons in L4 of the rat primary somatosensory (S1) area using the microelectrode, Carol Welker functionally demonstrated that one barrel corresponds to one whisker7. The anatomical map was developed in the barrel cortex based on the measurements of nerve activity. Then, Simons used a refined Carol's electrophysiological technique and clarified the detailed relation between barrels and whiskers[8]. Taken together, the cooperation of two different approaches (anatomical and physiological) resulted in the discovery of barrels.

About barrel cortex

Barrels

Barrel cortex is observed at the S1 area of many rodents (except for beavers and capybaras), such as mice, rats, hamsters, chinchillas, guinea pigs, squirrels, and porcupines. Moreover, the possum of the marsupial family also possesses a barrel cortex[9]. Each barrel is 100–400 μm in diameter and comprised of cortical cells located in a circular pattern around the clustered thalamocortical

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afferent. Barrel cells react to the tactile stimulation of contralateral mystacial vibrissae and process the acquired information. Though the development of the barrel cortex is independent of neural activity during early stages, the subsequent refinement of the brain map during the critical period is activity-dependent. While strong input enhanced by long-term potentiation (LTP) and information is stored, weak input is further weakened by long-term depression (LTD) and information is removed[10]. If mystacial vibrissae are ablated or removed during the critical period, the barrel corresponding to the removed vibrissae will disappear or become smaller in area. However, after the critical period, barrel structure remains unchanged even after whisker pruning. Therefore, the barrel map must receive input from vibrissae during the critical period (P0–5). The numbering of the arrangement in the projection maps and vibrissae were based on Dörfl's paper[11]. Thus, the whisker/barrel system is reorganized in an input-related fashion by neural plasticity during the developmental period. Therefore, the whisker/barrel system deserves its status as a model to study experience-dependent brain development.

Barrels and Septa

In the S1 area, there are barrel-related structures called "septa", the regions between barrels. Both barrels and septa are essential for information processing from vibrissae. Septa are low in cell density and display slow responsiveness to stimuli as compared with the barrels[12]. There are also significant differences between pyramidal neuronal structure located in barrels and septa. The former has a large spread of dendritic arborization, while the latter's dendritic tree is perpendicularly long.

Moreover, septa's cells possess narrow receptive fields and depolarizing responses of these cells are slower than barrel's cells. A barrel has a strong response to one particular whisker and is important in direction discernment of one whisker, while a septa responds to the stimulus from multiple whiskers[13]. In the neuronal circuit, a barrel column transfers passive sensory information from a whisker through the lemniscal system, while a septa column transfers active *kinaesthetic* information from a whisker through the extralemniscal system. Integration of these two kinds of information in the barrel cortex is important for the maturation of the whisker/barrel system.

Projection maps for vibrissae other than barrels

The projection maps for vibrissae are preserved not only in the cerebral cortex (barrels), but in the thalamus and trigeminal nucleus as well. There are barrelettes (name from the small sake barrel) in the ventrolateral nucleus of the nucleus sensorius principalis nervi trigemini (Pr5) and barreloids (name from the similitude of a sake barrel) in the dorsomedial nucleus of the thalamic VPM[14]. Moreover, lesser known, the barrelettes are also observed in the interpolar part of the spinal trigeminal nucleus (Sp5i)[15,16]. Although the barrel pattern for the upper jaw is well

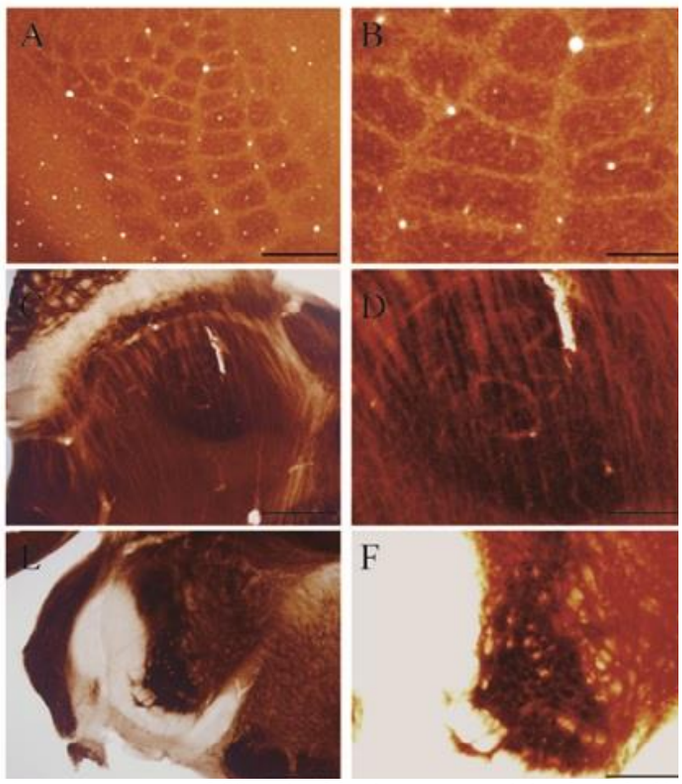

Figure 1: Images of CO-stained brain map containing barrels (A, B), barreloids (C, D) and barrelettes (E, F). (A–E) and (B–F): Low- and high-magnification images, respectively. Scale bars, (A–E) 500 μm and (B–F) 200 μm.

investigated, there are also barrel structures corresponding to the upper lip or the lower lip. If 240-μm–thick sections were prepared, two kinds of such barrel patterns are also observable in the barrelettes and barrels[17].

Recently, reported that the whisker-matched brain map formed by axons of L2/3 cells is present in the septa area of transgenic mice with GFP-labelled L2/3 cells, called the "barrel net"[18]. As is the case with barrels, the above three maps also correspond to individual whiskers, and are refined in an experience-dependent way during the critical period.

Synaptogenesis between thalamocortical axons and barrel cells in the S1 area

In the barrel unit in the S1 area, synapse formation between axon terminals from the VPM and barrel cells has been extensively investigated. Because glutamate is the transmitter of the somatosensory synapse and N-methyl-D-aspartic acid receptors (NMDARs) mediate LTP, NMDARs were studied first19. The morphological analyses using NMDAR antagonist-treated mice and cortex-specific NMDAR-knockout (KO) mice demonstrated that NMDAR-dependent LTP was critical for the development and experience-dependent plasticity of barrel cortices[20,21,22,23].

Moreover, protein kinase C (PKC), which is related to the induction and occurrence of NMDAR-dependent LTP[24,25], was reported to be engaged in the control of

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thalamocortical synaptic transmission onto L4 cells in the barrel cortex[26]. In particular, adenylyl cyclase 1 (AC1) is important for VPM neurons to form synapses[27]. Therefore, the NMDAR/AC1/PKA pathway is essential for synaptogenesis between barrel cells and thalamocortical axons (TCA) from the VPM. Furthermore, 5-hydroxytryptamine (5-HT) signalling is important for maturation of the barrel structure[28,29]. 5-HT released from raphe nuclei is taken up by the TCA serotonin transporter (5-HTT), packed by synaptic vesicles (VMAT2), and then activates 5HT1B (G-protein bound form serotonin 1B receptor). Moreover, because excessive 5-HT in the synaptic cleft inhibits the action of AC1 through the binding of 5-HT1B, excessive subcellular 5-HT, which is not packaged by VMAT2, is degraded by monoamine oxidase A (MAOA). The expression of 5HT1B and VMAT is high during the first 3 postnatal weeks in the TCA. Meanwhile, reduced 5-HT is also reported to be necessary for the formation of barreoids[30]. Therefore, 5-HT signalling is important for the maturation of synapses of the TCA.

On the other hand, mGluR5- and PLCβ-mutant mice displayed disrupted postsynaptic barrel patterns[31, 32]. Therefore, the mGluR5/PLCβ pathway is thought to be crucial for the postsynaptic regulation of barrel formation. Moreover, because germ line mutation for synaptic Ras-GTPase activating protein (GAP) resulted in the lack of the barrel cortex, the Ras pathway is also essential for the formation of the barrel cortex[33]. Furthermore, a glutamate transporter was also reported to be one of the important molecules that control critical period plasticity of barrel formation[34].

Thus, the cooperation between presynaptic and postsynaptic pathways matures synapses and develops the barrel cortex.

About visualising barrels

Although visualising barrels is important for analysing the whisker/barrel system precisely, it was too difficult to prepare correct sections obtained a complete view of each brain map. The way that barrels are arranged in L4 makes it difficult to obtain a global view using conventional slicing, like coronal, sagittal, and horizontal sections. As is the case with observational studies for other areas of the cerebral cortex (flat mounting method), the cerebral cortex is taken from the brainstem and extends keeping the L4 parallel to lab bench, and then kept pinned flat. If it is frozen in this state and the sectioning is performed, a section to observe the whole view of a barrel can be obtained (Figure 1A, B). It is the most difficult to obtain whole images of barreloids among the three brain maps. Like the barrels, full pictures of barreloids are grasped under general planes. Previously, the sectioning was performed under the following conditions: barreloids tilt at a 40-degree angle counter clockwise to the sagittal plane and lean at a 50-degree angle to the horizontal plane; rostral barreloids are inclined at a 30-degree angle[35,36] (Figure 1C, D). Finally, barrelettes are observed easily in coronal sections (Figure 1E, F). Two main types of staining methods enable visualisation of barrels. Nissl staining for L4 cortical neurons in the S1 area produces a postsynaptic pattern, while using enzymatic staining, such as for cytochrome oxidase (CO) or succinate dehydrogenase (SDH)[37], labels projection fibres from the thalamus, producing a presynaptic pattern. Each pattern is distinguishable with co-immunostaining (e.g. presynaptic, VGluT2 or postsynaptic, NeuN).

About vibrissae

In rodents, characteristic thick sensory hair grows on the skin of the mystacial pad. These hairs are about 0.1–0.2 mm in diameter in the rat as well as in the cat. The hair is tidily arranged according to a grid system and there is a large venous sinus surrounding the hair root. Therefore, the sensory hair is called a vibrissa (also known as a sinus hair). A thick capsule of connective tissue envelops the venous sinus. Various nerve endings are tightly distributed over the hair follicle wrapped hair axis. Predatory animals, rodents, and sirenians develop vibrissae. Because the acquirement of sensory information by vibrissae is essential for both development and refinement of the whisker/barrel system, mystacial vibrissae are an important receptive organ. Since the arrangement of vibrissae cannot change easily, it is used for individual recognition [38,39].

The arrector pili muscle surrounding a vibrissa capsule is composed of skeletal muscle and the nerve fibres derived from the facial nerve motor endplate on myofibres near a capsule. Thus, the facial nerve controls movement of the vibrissae. On the other hand, sensation is carried by the trigeminal nerve[40]. Nerve endings are at the tip of a nerve fibre without a myelin sheath. It is comprised of axon terminals and the terminal Schwann cell. The nerve endings of a hair follicle weave sensory endings (multiple axial fibres are bundled in one Schwann cell) with autonomic endings (an axial fibre alone is wrapped in a Schwann cell) and can be categorised into 6 general groups as follows: Merkel's discs, lanceolate endings, club endings, teledendrites, simple corpuscles, and free nerve endings. Merkel's discs are subdivided into epidermis and hair follicle-types. The former is a disc located at the basolateral surface of the Merkel cell, while the latter is a disc contacting the corneum side of the Merkel cell. While Merkel's discs and simple corpuscles are slowly adapting mechanoreceptors, lanceolate endings, club endings, and teledendrites are rapidly adapting mechanoreceptors[41]. As Munger and Ide advocated in 1988, axonal spines were thought to transform a mechanical stimulus into electrical excitation[42]; axonal spines are the cytoplasmic excrescences protruding from axon terminals between Schwann sheaths. Electron microscopy demonstrated that axonal spines existed in all the mechanical receptors except the Merkel's disk[43,44]. A wide variety of nerve endings in a hair follicle enable vibrissae to sense various environmental alterations. Hence, vibrissae are the essential sensory organ for rodents.

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About the pathway of sensory information obtained from vibrissae

The pathway of sensory information obtained from vibrissae is well understood[45]. Sensory information is received by the various sensory receptors in the roots of vibrissae and conveyed to Pr5 and Sp5i through the primary afferent fibre of the trigeminal ganglia (TG). Output fibres of trigeminal nuclei make synaptic contacts with the neurons in the dorsomedial part of the VPM and the medial division of posterior nucleus (POm) across the midline. The axons of VPM and POm neurons project to barrel cortex. In the above-mentioned pathway, a distinction is generally made between the lemniscal and paraleminiscal pathways. Sensory information arrives at the barrel columns through Pr5 and VPM in the lemniscal pathway, while kinetic information reaches septa columns through Sp5i and POm in the paraleminiscal pathway. Rostral Sp5i neurons transmit tactile sensation to POm, and caudal transmit other sensations (thermal, pain) to the ventrolateral part of the VPM[46]. The latter is called paraleminiscal pathway and information arrives at the secondary somatosensory (S2) area. Incidentally, the zona incerta (ZI) is also projected from Sp5i and the signal to the primary motor area from POm is regulated by the disinhibition of the ZI. Information from both pathways is thought to be integrated in the barrel area. Information is then conveyed to L2/3 and fed back to L4. Moreover, information arriving at L4 feeds back to the VPM through L6.

On the other hand, Pr5 is suppressed by whisker whisking controlled by facial nuclei through Sp5i. The neurons of the somatosensory area project to Sp5i neurons directly, but the neurons of the motor area do not. Thus, Sp5i neurons are controlled by whisker vibration. Motoneuronal regulation of Pr5 neurons is controlled by large pyramidal neurons in the L5 of the S1 area[47].

About development of the whisker/barrel system

Vibrissae

The regular arrangements of epidermal primordia on the mystacial pad mature into whisker follicles from embryonic day 12 (E12) to E16. The progenitor cells that develop into follicles arise from epidermal cells and are classified into the outer root sheath and the germinative matrix. The outer root sheath emerges as part of the epidermis by E14, and the hair bulb is also derived from the epidermis. On the other hand, the germinative matrix covered by the hair bulb produces the inner root sheath and hair shaft by E16[48,49]. Moreover, the formation of the vibrissal capsule is followed by the outer and inner root sheath formation and the various sensory endings are continuously formed according to the development of the vibrissae: Merkel endings at E13.5, lanceolate endings at E16.5, and Ruffini endings, reticulate endings and transverse lanceolate endings at P7[50].

TG

The neuropoietic period is from E8.5 to E13[51,52,53]. The maxillary axons (ION) of trigeminal nerves begin to extend at E10 and innervate the whisker pad at E10.5. On the other hand, TG axons arrive at PrV in the brainstem at E12. The gross topographic pattern formed by the trigeminal projection to the whisker pad begins at E12 and is completed by E13[54,55].

Pr5

As soon as Pr5 neurons appear in the ventricular zone of the ventral part of the metencephalon at E10.5, their axons intersect at the midline. Pr5 neurons migrate ventrolaterally towards the areas next to the TG at E11.5.The Pr5 area is completely formed at E15. The axons of Pr5 arrive at midbrain at E15, reach the VPM at E17, and then form lines in the VPM from E18 to P0. First, the invasion of axons is diffuse and redundant, and then the arrangement of axons becomes orderly[56]. Barrelette patterns appear in the Pr5 from P0 to P1.

VPM

Neurogenesis in the dorsal thalamus occurs from E10.5 to E14.5. TCA from the VPM is elongated towards the cerebral cortex tangentially through medial and lateral ganglionic eminence, and then reach the somatosensory area at E15[57]. As for TCA outgrowth, invasion of the hypothalamus and midbrain crossing is inhibited by Slit and various other factors (e.g. Netrin-1, LAMP, ephrin/Eph receptor, etc.). On the way towards the cerebral cortex, TCA comes in contact with subplate neurons, which are important to form the sensory map in rodents and in the primitive striatum, and is guided by interactions with subplate neurons. TCA terminals become aligned in the primary somatosensory area at P3. Barreloid patterns emerge in the VPM at P3.

S1 area

During E14 and E15, L4 neurons are generated in the somatosensory cortex. The critical period of structural plasticity lasts until P4 (barrels) or P5 (barrel nets), and the cytoarchitectonic structure of the barrel area is fully formed from P5 to P7[58]. The critical period of synaptic plasticity between L4 neurons and L2/3 neurons lasts from P10 to P14[59, 60]. Active whisking begins along with eye opening[61]. The critical period for horizontal connections between L2/3 neurons is from P13 to P16[62].

Discussion

The author has referenced some of his own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

Humans do not require vibrissae, given our developed sense of touch and vision. Indeed, in primates, vibrissae tend to degenerate since primates evolved a nail instead of a claw, and with it, the feeling of the fingertip became

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highly sensitive. Therefore, it seems that vibrissae became unnecessary in primates. In contrast, the vibrissae of rodents are very important sensory organs comparable to the human fingertip and the whisker/barrel system is essential for survival. The whisker/barrel system is useful as a model of activity-dependent development in neural circuits because the development of barrels requires whisker input during postnatal weeks. Recently, interest in the relationship between neurons and glia has led to studies of barrel cortical neurons and glia, revealing their intimate link[63,64]. While much is known about the barrel cortex, there are still unanswered questions, especially related to the detailed mechanism regulating the barreloids in the VPM.

To date, morphological alteration of barrel patterns was observed in various KO mice. For example, cortex specific-NR1KO mice[23], mGluR5-KO mice[65], PLC-β-KO mice[66], and PKARIIβ-KO mice[67].They all display improper postsynaptic barrel patterns. On the other hand, AC1-KO mice[27], 5-HTT-KO mice[68], MAOA-KO mice[68], and GAP-43-KO mice[69] have no barrel formation at all. Thus, postsynaptic aberrations result in abnormal barrels, while presynaptic aberrations result in barrels and TCA terminals that are out of alignment, leading to the lack of barrel patterning. These findings suggested that arrival of TCA in the barrel cortex leads to the array of barrel cells and confirmed that the maturation of the TCA from the VPM is essential to form the barrel cortex. On the other hand, for example in Drg11- or Lmx1b-KO mice, barrelette pattern is defective and there is a loss of both barreloid and barrel patterns[70]. Further, the short axonal growth of TG resulted in defective barrelettes[71]. In this way, the maturation of the upstream structure was conducive to the development of the downstream structure in the whisker/barrel system. The whisker/barrel system originates from information from vibrissae. Reportedly, the loss of vibrissae led to defects of barrelettes[72]. Therefore, more studies on vibrissae and how they control patterning in the brain are required.

Conclusion

The information entering the vibrissae of the rodent sensory receptor is transmitted to the brainstem through the trigeminal ganglion, and then reaches the somatosensory area. The brain maps corresponding to individual vibrissae are conserved at the cerebral cortex (barrel) and the brainstem (barrelette, barreloid) levels. This brain map is refined by sensory information received at a critical period after birth. Since the brain map can be visualised, this map can be investigated anatomically as well as electrophysiologically. Given all the advantages and knowledge about the barrel cortex, questions about how neurons develop and wire together, and how experience can shape neural circuits should be investigated using this model neural circuit.

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