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What can we get from 'barrels': the rodent barrel cortex as a model for studying the establishment of neural circuits

Chia-Shan Wu,[1,2] Carlos J. Ballester Rosado[1,2,3] and Hui-Chen Lu[1,2,3,4]
[1]The Cain Foundation Laboratories, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston, TX, USA
[2]Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
[3]Program in Developmental Biology, Baylor College of Medicine, Houston, TX, USA
[4]Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA

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Abstract

Sensory inputs triggered by external stimuli are projected into discrete arrays of neuronal modules in the primary sensory cortex. This whisker-to-barrel pathway has gained in popularity as a model system for studying the development of cortical circuits and sensory processing because its clear patterns facilitate the identification of genetically modified mice with whisker map deficits and make possible coordinated *in vitro* and *in vivo* electrophysiological studies. Numerous whisker map determinants have been identified in the past two decades. In this review, we summarize what have we learned from the detailed studies conducted in various mutant mice with cortical whisker map deficits. We will specifically focus on the anatomical and functional establishment of the somatosensory thalamocortical circuits.

Introduction

In cortical sensory maps, thalamocortical afferents (TCAs) transmit peripheral sensations in organized arrays into distinct cortical neuronal modules to provide a topographic representation of the external sensory world (Buonomano & Merzenich, 1998). Mis-wiring of neuronal circuits during early life is likely to be a major cause of neurological disorders, including autism and schizophrenia, which may arise from defects in cortical development (Calhoun *et al.*, 2009; Luscher & Huber, 2010; Rubenstein, 2011). The rodent whisker map in the primary somatosensory cortex (S1; Fig. 1) has emerged as a popular model system for elucidating the molecular mechanisms underlying the formation of cortical neural circuits as well as for exploring how sensory experience affects the development of neural networks (Erzurumlu & Kind, 2001; Feldman & Brecht, 2005; Fox & Wong, 2005; Inan & Crair, 2007; Petersen, 2007; Fox, 2008).

In this review, we focus on the molecular determinants of mouse cortical whisker map formation and their roles in neuronal morphogenesis and synaptic function and plasticity. First, the developmental processes occurring during embryonic and early postnatal ages that lead to the formation of 'barrels', neuronal modules in S1 representing individual whiskers, as informed by studies conducted with mice, will be described. Next, the distinctive characteristics of the whisker map deficits found in a variety of genetically modified mice (transgenic mice) will be summarized. This section will focus on how specific mutations affect the arborization pattern of thalamocortical axons and the dendritic morphogenesis of cortical layer IV glutamatergic neurons within S1. Finally, the functional development of thalamocortical synapses will be discussed in wildtype and mutant mice with cortical whisker map deficits.

Correspondence: Hui-Chen Lu, [1]The Cain Foundation Laboratories, as above.
E-mail: hclu@bcm.edu

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The rodent whisker-to-barrel pathway

Rodents have poor vision and depend on tactile information derived from whiskers on their snout to navigate through their environment. Facial whiskers are innervated by the infraorbital branch of the trigeminal nerve (ION). The central afferents of these primary sensory neurons innervate brain stem trigeminal nuclear complex (BSTC), including the rostral principal nucleus (PrV) and the caudal spinal nucleus (SpV) (Fox, 2008; Erzurumlu *et al.*, 2010; also Fig. 1). The spatial arrangements of neuronal modules for individual whiskers in the BSTC, named 'barrelettes', are arranged into a row-and-arc pattern recapitulating arrangement of the facial whiskers. Trigeminothalamic axons from the PrV project to the contralateral thalamic ventral posteromedial (VPM) nucleus, via the lemniscal pathway. In VPM they form the whisker-related pattern called 'barreloids' with an inverted orientation. The TCAs of VPM innervate S1 and form whisker-related clusters in cortical layer IV. Each TCA cluster relaying sensory information from an individual whisker is encircled by a distinctive ring of cortical layer IV neurons (barrels; Woolsey & Van der Loos, 1970; Killackey & Leshin, 1975). Barrelettes in the BSTC begin to appear at late postnatal day (P)0 (Li *et al.*, 1994) or P1 (Ma, 1993) depending on the mouse strain. Around P3, barreloids and barrels begin to develop in the thalamus (Woolsey, 1990) and S1 (Rebsam *et al.*, 2002), respectively. Sensory information from individual whiskers is relayed to the corresponding barrelette, barreloid and barrel in a clear one-to-one relationship.

The developing axons of trigeminal ganglion neurons are guided by a combination of molecular cues to target their peripheral and central targets and sculpt their synaptic connections to form the whisker map (reviewed in Erzurumlu *et al.*, 2010). The identified positional cues that lay out the rough topography include various neurotrophins, axon guidance molecules, transcription factors and glutamate receptors. Loss-of-function mutation in the gene encoding *Drg11*, a paired-

domain transcription factor expressed in the principal nucleus of BSTC but not in the thalamus or cortex, results in the absence of whisker map throughout the whisker-to-barrel pathway (Ding *et al.*, 2003). Interestingly, mutant mice with extra whiskers have extra barrels in the corresponding locations (van der Loos & Dorfl, 1978; Van der Loos *et al.*, 1984). These findings suggest that the spatial layout in the principal brainstem nucleus, the first sensory relay station, forms the basis for the whisker map in higher sensory stations. The refinement of sensory maps and the establishment of precise stimulus–response features, however, may depend on other cellular and synaptic processes that rely, at least in part, on neural activity-dependent mechanisms (Katz & Shatz, 1996; Crair, 1999).

In addition to the lemniscal pathway, sensory information derived from whiskers can also be relayed to the cortex through the paralemniscal pathway (Petersen, 2007; Fox, 2008). Here, sensory afferents from SpV in the BSTC project to the posteriomedial nucleus of thalamus (POm), and then POm TCAs innervate the inter-barrel septal area of S1 layer IV. In this review we have focused on the lemniscal pathway because it is the major whisker-to-barrel pathway.

The development of reciprocal connections between the thalamus and the cortex

Thalamic axons projecting into the cortex relay sensory inputs, while reciprocal innervations from the cortex to the thalamus provide critical feedback to modulate the thalamic responses required for the complex information processing and integration that underlie cognitive behaviors (Jones, 2002; Alitto & Usrey, 2003; Temereanca & Simons, 2004; Theyel *et al.*, 2010). Around embryonic day (E)13 (Fig. 2), TCAs derived from the dorsal thalamus begin to project ventrally and then turn dorsolaterally at the boundary between the diencephalon and the telencephalon (Lopez-Bendito & Molnar, 2003; Price *et al.*, 2006). At E13.5, TCAs pass through a restricted but permissive corridor between the lateral and medial ganglionic eminences (LGE and MGE) as tight bundles (Molnar *et al.*, 1998). This corridor is formed by a special population of GABAergic neurons, called guidepost cells, originating from the LGE and migrating to the mantle region of the MGE (Lopez-Bendito *et al.*, 2006). After entering striatum proper, TCAs separate into multiple fascicles and reach the pallial–subpallial boundary (PSPB). In the mean time, corticothalamic axons (CTAs), originating from preplate principal neurons, leave the cortical plate and extend to the PSPB (Jacobs *et al.*, 2007). It has been proposed that the PSPB is a critical region for the reciprocal interactions between the TCAs and CTAs (Molnar & Butler, 2002). Deleting the transcription factor Pax6 in this area causes aberrant routing of many TCAs and CTAs (Simpson *et al.*, 2009). After a period of potential interaction between TCAs and CTAs in the PSPB, the respective axons resume their progression toward their specific targets.

The long-distance navigation of TCAs and CTAs towards their targets involves an elaborate coordination of multiple factors that initiate and guide axon outgrowth, fasciculation, navigation, target recognition and refinement (Katz & Constantine-Paton, 1988; Molnar *et al.*, 2003; Garel & Rubenstein, 2004; Price *et al.*, 2006; Inan & Crair, 2007). Several ligand-and-receptor (ligand/receptor) families involved in axon guidance have been identified (reviewed in O'Donnell *et al.*, 2009). These include semaphorins/plexin and neuropilin, ephrins/Eph, netrins/DCC and UNC5, and Slits/Robo. Slit2 is expressed in the hypothalamus and its activity repel the Robo-expressing guidepost cells that form the corridor for TCAs (Bielle *et al.*, 2011). Thus they prevent TCAs from erroneously entering the hypothalamus and from crossing the midline (Bagri *et al.*, 2002; Braisted *et al.*, 2009). A 'handshake hypothesis' for TCA and CTA interactions has been postulated based on the close association of these tracts (Molnar & Blakemore, 1995), and the observation that deleting a particular transcription factor expressed only in the cortex or only in the thalamus leads to abnormalities of both tracts (Hevner *et al.*, 2002). This hypothesis posits that corticothalamic and thalamocortical axons serve as scaffolds for each other and axon–axon interactions are important for the correct patterning and targeting of these axons. Recently, we found that removing cannabinoid receptor type 1 (CB_1R) from cortical glutamatergic neurons leads to morphological changes in both CTAs and TCAs (Wu *et al.*, 2010). These observations suggest that endocannabinoid signaling may be a modulator of the handshake interactions between CTAs and TCAs, especially for the interactions mediating the fasciculation process.

The subplate (SP) neurons, which are among the first born-cortical neurons, send 'pioneer' axons to meet TCAs in the PSPB, and defects in SP neurons lead to failure of TCA innervation of the cortex (McConnell *et al.*, 1989; Zhou *et al.*, 1999; Kanold & Luhmann, 2010). Once TCAs reach the cortex at ~E15 (Molnar *et al.*, 1998) they pause in the SP layer and then begin innervating the cortex at ~P0. Whether early neural activity is required for correct TCA targeting is still controversial. Genetic ablation of SNAP25, a protein that is involved in evoked neurotransmitter release, did not affect the growth, targeting or innervation of TCAs into S1 during embryonic development (Molnar *et al.*, 2002). This suggests that TCA growth, early topographic sorting of these fibers and innervation into cortex does not rely on activity-dependent mechanisms requiring evoked neurotransmitter release.

The development of the whisker map in S1

Barrels, the neuronal modules representing whiskers, can be easily identified as periodic, cell-dense walls separated by a cell-sparse area in cortical layer IV of S1. During postnatal development, TCAs reach layer IV and VI neurons immediately after birth (Rebsam *et al.*, 2002). At P2, TCAs in the cortex separate into two loosely distributed bands, one in layer VI and one in layer IV (Rebsam *et al.*, 2002). At P3, when TCAs begin to segregate into whisker-related clusters in layer IV, the distributions of dendrites projecting out from individual spiny stellate neurons are minimally polarized (Espinosa *et al.*, 2009). At P4, the whisker map can also be revealed by the distribution of postsynaptic molecules such as protein kinase A (PKA) regulatory subunit IIβ (PKARIIβ; Watson *et al.*, 2006), metabotropic glutamate receptor 5 (mGluR5; Wijetunge *et al.*, 2008) and Fragile X mental retardation protein (FMRP; Harlow *et al.*, 2010). At P5, glial processes revealed by immunoreactivity to either of the glutamate transporters GLAST or GLT-1 also distribute in a whisker-related manner (Voutsinos-Porche *et al.*, 2003). At P6, the time when the barrel ring is just beginning to form, spiny stellate neurons develop a polarized dendritic pattern (Espinosa *et al.*, 2009). After P6, the dendritic segment number of layer IV neurons and the complexity of TCA arbors continue to rise until the end of the second postnatal week.

Molecular determinants of whisker map formation

The prominent anatomical features of barrels have facilitated the identification of several mutant mice with defective whisker maps in S1 (Erzurumlu & Kind, 2001). In this review, we will focus on the mutant mice that have normal cortical laminations and normal axonal targeting (Table 1). There are two types of whisker map deficits found in these mutant mice and they can be distinguished based on the

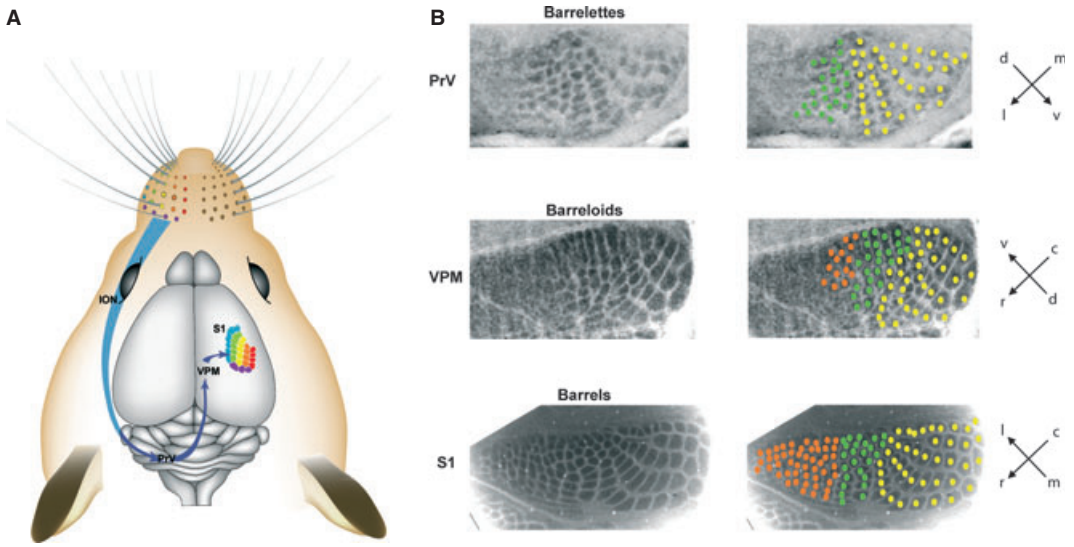

FIG. 1. The lemniscal whisker-to-barrel pathway in the mouse brain. (A) The whiskers on the snout are innervated by the infraorbital branch of the trigeminal nerve (ION), which transmit sensory information to the rostral principal nucleus (PrV) in the brainstem. Trigeminothalamic axons from the PrV project to the ventral posteromedial nucleus (VPM) in the thalamus in the contralateral hemisphere. Thalamocortical axons from the VPM project to the primary somatosensory cortex (S1). The five rows of whiskers and the straddle whiskers are color-coded. (B) Representative images of cytochrome oxidase (CO)-stained coronal sections through PrV of brain stem (barrelettes) and VPM of thalamus (barreloids), and tangential sections through cortical layer IV (barrels). CO patches corresponding to rostroventral whiskers are marked with orange and green circles, and caudodorsal whiskers with yellow circles. Drawing in A is modified from an Adobe Illustrator file generously provided by Knott *et al.* (2002).

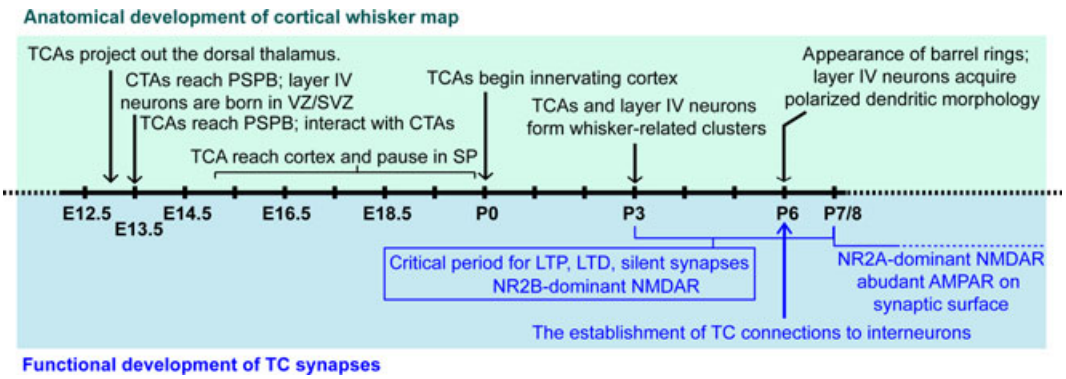

FIG. 2. Timeline for development of the mouse cortical whisker map.

characteristics of their pattern deficits. The first type is the complete absence of whisker map. This group includes, but is not limited to, the null mutant mice of the following genes: *N*-methyl-D-aspartate receptor (NMDAR) subunits 1 and 2B (NR1 and NR2B; Li *et al.*, 1994; Kutsuwada *et al.*, 1996; Iwasato *et al.*, 1997), AC1 (adenylyl cyclase I; *Adcy1*^{brl}) (Welker *et al.*, 1996), monoamine oxidase A (MAOA; Cases *et al.*, 1996) and serotonin (5-HT) transporter (5-HTT; Persico *et al.*, 2001; Salichon *et al.*, 2001). In other mutant mice, the organization of layer IV neurons and whisker-related TCA clusters are 'mismatched' with complete absence of the architectonic organization of layer IV neurons while the whisker-related TCA clusters are visible. This group contains the null mutant mice of mGluR5 (Wijetunge *et al.*, 2008; She *et al.*, 2009), phospholipase C-β1 (Hannan *et al.*, 2001), PKARIIβ (Inan *et al.*, 2006; Watson *et al.*, 2006), SynGAP, a synaptic Ras GTPase activating protein (Barnett *et al.*, 2006), Neurogenic Differentiation 2 (NeuroD2; Ince-Dunn *et al.*, 2006) and LIM domain-only 4 (LMO4; Kashani *et al.*, 2006). It also includes cortex-specific (Cx-) knockouts (KOs) of NR1, mGluR5 (Iwasato *et al.*, 2000; Ballester-Rosado *et al.*, 2010) and neurofibromin (NF1) (Lush *et al.*, 2008). The nature of mutations leading to whisker map deficits suggest that glutamatergic and serotonergic neurotransmission, cAMP–protein kinase A (PKA) signaling, phospholipase C–inositol 1,4,5-trisphosphate (IP3) signaling, and activity-dependent transcription are all involved in barrel development.

The 5-HT afferents arising from the raphe nuclei of the brain stem innervate S1 early in development, coinciding with the clustered ingrowth of thalamocortical fibers (Bennett-Clarke *et al.*, 1993). 5-HT released into the thalamocortical synaptic cleft is taken up by TCAs via the 5-HTT and packed into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2) (Lebrand *et al.*, 1996, 1998; Cases *et al.*, 1998). 5-HT not packed into vesicles is degraded by MAOA, an enzyme that catalyzes the oxidative deamination of monoamines. 5-HT can activate the G-protein-coupled 5-HT1B receptor on TCAs, and has been reported to inhibit the release of glutamate (Rhoades *et al.*, 1994; Laurent *et al.*, 2002). Deleting either MAOA or 5-HTT genes in mice results in excess 5-HT in S1 and

TABLE 1. Mutant mice with whisker map deficits

Protein	Gene name	Global or Cx-KO	Barreletts in BSTC	Barreloids in thalamus	Whisker-related TCA clusters in S1	Barrels in S1	Synaptic function and plasticity	References
Adenylyl cyclase 1	Adcy1	Global	Normal	Small barreloids not well delineated	No whisker-related pattern; single TCA analysis found normal axonal length, branch and bouton numbers while axonal spans were larger	No whisker-related pattern	Defective glutamatergic release, AMPAR trafficking, and long-term plasticity in thalamocortical synapses. *In vivo* single unit recording revealed normal topography for whisker map despite a decrease in the response latency for surrounding whiskers	Welker *et al.* (1996) Abdel-Majid *et al.* (1998) Lu *et al.* (2003) Gheorghita *et al.* (2006) Lu *et al.* (2006)
Adenylyl cyclase 1	Adcy1	Cx- by EMX-Cre	Normal	Normal	Normal	Barrels are evident but layer IV spiny stellate neurons have reduced dendritic asymmetry and increased dendritic span	AMPA/NMDA current ratio is reduced at P11; reduced amplitude of evoked AMPA-mediated currents	Iwasato *et al.* (2008)
cAMP-dependent protein kinase type II regulatory subunit	Pka-R2	Global	Normal	Normal	Normal	No whisker-related pattern	Impaired thalamocortical LTP formation and AMPAR trafficking	Inan *et al.* (2006) Watson *et al.* (2006)
NMDA receptor subunit 1	Grin1	Global	No whisker-related pattern	No whisker-related pattern	No whisker-related pattern	No whisker-related pattern	Evoked NMDAR-responses are reduced in layer IV neurons of S1	Li *et al.* (1994) Iwasato *et al.* (1997) Rudhard *et al.* (2003)
NMDA receptor subunit 1	Grin1	Cx- by EMX-Cre	Normal	Normal	TCAs form rudimentary pattern for caudodorsal whiskers; analysis of single TCA shows reduced branching and reduced total axon arbor length but wider distributions	No whisker-related pattern; layer IV spiny stellate neurons have symmetric dendritic morphology and their dendritic spans, total dendritic lengths, and spine numbers are increased	NA	Datwani *et al.* (2002) Lee *et al.* (2005) Iwasato *et al.* (2000)
NMDA receptor subunit 2B	Grin2b	Genetic mosaic*	NA	NA	NA	KO neurons have symmetric dendritic morphology	NA	Espinosa *et al.* (2009)
Metabotropic glutamate receptor 5	Grm5 or Mglur5	Global	Small barreletts not well delineated	Small barreloids not well delineated	TCAs form rudimentary pattern for caudodorsal whiskers; analysis of single TCA shows reduced complexity and reduced total axon arbor length while the axonal span is increased	No whisker-related pattern; layer IV spiny stellate neurons have symmetric dendritic morphology and increased dendritic span	Abnormal thalamocortical LTP/LTD formation; faster NMDA current decay kinetics; normal presynaptic function; mEPSC frequency is increased while mIPSC frequency is reduced	Hannan *et al.* (2001) Wijetunge *et al.* (2008) She *et al.* (2009) Ballester-Rosado *et al.* (2010)

TABLE 1. (Continued)

Protein	Gene name	Global or Cx-KO	Barreletts in BSTC	Barreloids in thalamus	Whisker-related TCA clusters in S1	Barrels in S1	Synaptic function and plasticity	References
Metabotropic glutamate receptor 5	Grm5 or Mglur5	Cx- with NEX-Cre	Normal	Normal	TCAs form rudimentary pattern for caudodorsal whiskers; analysis of single TCA shows reduced complexity and reduced total axon arbor length while the axonal span is increased	No whisker-related pattern; layer IV spiny stellate neurons have symmetric dendritic morphology and increased dendritic span and segment numbers	mIPSC frequency is reduced while mEPSC frequency is normal	Ballester-Rosado *et al.* (2010)
Phospholipase C, beta1	Plcb1	Global	NA	NA	Normal	No whisker-related pattern	NA	Hannan *et al.* (2001)
Synaptic Ras GTPase-activating protein 1	SynGAP1	Global	Normal	Small barreloids are not well delineated	Rudimentary pattern for caudodorsal whiskers	KO: no whisker-related pattern; HET: reduced barrel segregation	NA	Barnett *et al.* (2006)
Monoamine oxidase type A	MAOA	Global	Normal	Small barreloids are not well delineated	No whisker-related pattern or rudimentary pattern for caudodorsal whiskers	No whisker-related pattern	NA	Cases *et al.* (1996)
Sodium-dependent 5-HT transporter	SERT; 5-HTT	Global	KO: barreletts poorly defined; HET: small barreletts that are not well delineated	KO: barreloids are poorly defined, VPM is smaller; HET: barreloids are not well delineated	KO: no whisker-related pattern except a rudimentary pattern for a few large caudal whiskers; HET: blurry boundaries for TCA clusters	KO: no whisker-related pattern; HET: septa between barrels are larger	NA	Persico *et al.* (2001)
Monoamine oxidase A; 5-HT transporter	MAOA; 5-HTT	DKO	NA	Small medioventral barreloids are poorly delineated	No whisker-related pattern	No whisker-related pattern	NA	Salichon *et al.* (2001)
Monoamine 1B oxidase A; 5-HT receptor	MAOA; 5-HT1B	DKO	NA	Normal	Normal	Fuzzy whisker-related pattern with reduced barrel segregation	NA	Salichon *et al.* (2001)
MAOA; 5-HTT; 5-HT1B TKO	MAOA; 5-HTT; 5-HT1B	TKO	NA	NA	Normal	Fuzzy whisker-related pattern with reduced barrel segregation	NA	Salichon *et al.* (2001)
LIM domain transcription factor LIM domain-only 4	Lmo4	Cx-with NEX-Cre	NA	NA	TCAs form rudimentary pattern for caudodorsal whiskers	No whisker-related pattern	NA	Kashani *et al.* (2006)

TABLE 1. (Continued)

Protein	Gene name	Global or Cx-KO	Barreletts in BSTC	Barreloids in thalamus	Whisker-related TCA clusters in S1	Barrels in S1	Synaptic function and plasticity	References
Neurogenic differentiation factor 2	NeuroD2	Global	Normal	Normal	Rudimentary pattern for caudodorsal whiskers	No whisker-related pattern	Reduced AMPA/NMDA current ratios and reduced spontaneous EPSC amplitude	Ince-Dunn *et al.* (2006)
Brain-derived neurotrophic factor	BDNF	Global	NA	NA	Delayed appearance of whisker pattern	NA	Reduced AMPA/NMDA current ratios; defective LTP formation and increased the number of silent synapses in thalamocortical synapses; altered development of fast-spiking GABAergic neurons	Itami *et al.* (2003) Lush *et al.* (2005) Itami *et al.* (2007)
Neurotrophic tyrosine kinase receptor type 2	NTRK2; TrkB	Global	NA	NA	Delayed appearance of whisker pattern	NA	NA	Lush *et al.* (2005)
Neurotrophic tyrosine kinase receptor type 2	NTRK2; TrkB	Cx- with hGFAP-Cre	NA	NA	Normal	NA	NA	Lush *et al.* (2005)
EphrinA5	EFNA5	Global	NA	NA	Normal whisker-related pattern but the number and length of TCA arbors are reduced	NA	NA	Uziel *et al.* (2008)
Neurofibromin	Nf1	Cx- with hGFAP-Cre	NA	NA	Smaller TCA clusters and bigger septa area	No whisker-related pattern	NA	Lush *et al.* (2008)

Protein names and gene names are based on http://www.uniprot.org. Cx-, cortex-specific; HET, heterozygous; DKO, double KO; TKO, triple KO.

barrel map deficits (Cases *et al.*, 1996; Persico *et al.*, 2001). Deleting 5-HT1B receptors in either MAOA- or 5-HTT-KO mice rescues the barrel map deficit in these mutants (Salichon *et al.*, 2001), suggesting that 5-HT1B receptor hyperactivity disrupts barrel map formation. However, the incomplete rescue of barrel cytoarchitecture in MAOA- or 5-HTT-KO mice by 5-HT1B removal suggests that additional mediators of 5-HT signaling in S1 define barrel pattern. Conversely, the normal whisker map in 5-HT1B-KO mice suggests that 5-HT signaling through 5-HT1B receptors is not required for barrel formation under physiological condition (Salichon *et al.*, 2001).

Ectopic expression of fibroblast growth factor (FGF) in cortical neurons leads to duplication of barrel fields (Fukuchi-Shimogori & Grove, 2001) and TCA patterns are defective in both Cx-NR1- and Cx-mGluR5-KO mice (Iwasato *et al.*, 2000; Ballester-Rosado *et al.*, 2010). These latter findings argue that factors intrinsic to the cortex also instruct TCA patterning. Nevertheless, the rudimentary whisker-related TCA patterns in Cx-NR1- or Cx-mGluR5-KOs argue against an absolute requirement for postsynaptic NMDAR and mGluR5 activity in guiding the somatotopy of TCAs. It is likely that TCAs themselves play an instructive role in segregating TCAs into whisker-related clusters.

In the adult S1, neurons located in a particular barrel receive sensory input predominantly from their principal whisker (Welker, 1976; Simons & Woolsey, 1979; Armstrong-James & Fox, 1987; Welker *et al.*, 1993). In '*barrelless*' *Adcy1*^{brl} mice (Van der Loos *et al.*, 1986), the cytoarchitectonic features characteristic of barrels are missing in the cortex, and the distribution of thalamocortical afferents is continuous over an area of up to ten presumptive barrels (Welker *et al.*, 1996). *In vivo* single-cell recordings from the presumptive barrel field of *barrelless* mice show that layer IV neurons have somatotopically appropriate receptive fields for their principal whiskers but also respond to neighboring whiskers with short latency. In mGluR5-KO mice, barrel rings are missing but the representations for large whiskers are identifiable as clusters of TCAs. Recordings of whisker-evoked activity also found preserved topographical organization of facial vibrissae in mGluR5-KO mice, but a significantly diminished temporal discrimination of center to surround whiskers in the responses of individual neurons (She *et al.*, 2009). These results suggest that the cortical representations for individual whiskers are grossly preserved in S1 of these mutant mice despite the absence of barrel cytoarchitecture.

Whisker-related arborizations of single TCAs

In the adult, TCAs arborize in cortical layers IV and VI with densely segregated clusters of arbors in layer IV and a loosely diffuse pattern in layer VI (Agmon *et al.*, 1995; Rebsam *et al.*, 2002; Lee *et al.*, 2005). Anatomical studies of individual TCAs at different developmental stages (Rebsam *et al.*, 2002; Lee *et al.*, 2005) found that at P2-3 TCAs innervating the barrel field have relatively diffuse projection patterns. After P6-7, individual TCAs form highly branched and densely clustered arbors corresponding to the mapped facial whisker. These observations suggest that a progressive addition of branches at the appropriate cortical location with the commensurate elimination of inappropriate branches leads to the formation of whisker-related TCA arborizations (Senft & Woolsey, 1991; Rebsam *et al.*, 2002).

In both global- and Cx-mGluR5-KO mice, TCAs formed significantly fewer branches but spanned a wider area (Fig. 3; also Ballester-Rosado *et al.*, 2010). The total lengths of their axonal arbors were also significantly shorter. These data suggest that mGluR5 signaling in cortical glutamatergic neurons instructs TCAs to develop a compact and highly branched axonal patterning in layer IV. Similar to Cx-mGluR5-KO mice, cortex-specific removal of NR1 also leads to rudimentary TCA patterns (Iwasato *et al.*, 2000; Datwani *et al.*, 2002). However, in contrast to the reduced TCA complexity in mGluR5-KO mice, single TCAs in Cx-NR1-KO mice have exuberant branches (Lee *et al.*, 2005). Thus, mGluR5 and NMDAR exert different effects on TCA arborization.

The TCA patterning deficits observed in Cx-mGluR5- and Cx-NR1-KO mice suggest that retrograde signaling induced by glutamate receptors plays an important role in guiding the growth of TCAs into a compact and highly branched pattern in their corresponding barrels. Several activity-dependent retrograde messengers made postsynaptically and acting presynaptically have been identified (for review see Regehr *et al.*, 2009), including endocannabinoids, nitric oxide, neuropeptides, neurotransmitters (e.g., glutamate), trophic factors [e.g. brain-derived neurotrophic factor (BDNF)], ephrin/Eph, etc. Many studies have found that mGluR5 signaling regulates the postsynaptic synthesis of endocannabinoids and BDNF to modulate neurotransmission presynaptically. BDNF and several ephrin/Ephs are expressed in the developing S1 (Itami *et al.*, 2000; Vanderhaeghen *et al.*, 2000; Bolz *et al.*, 2004) and *in vitro* studies found that BDNF and ephrin/Eph can promote TCA branching (Gao *et al.*, 1998; Mann *et al.*, 2002; Hanamura *et al.*, 2004). Despite a grossly normal whisker map in S1, the complexity of TCA arbors is reduced in Ephrin–A5-KO mice (Vanderhaeghen *et al.*, 2000; Uziel *et al.*, 2008). In BDNF-KO and tyrosine kinase receptor type 2 (TrkB)-KO mice, a delayed TCA clustering has been reported (Lush *et al.*, 2005). Therefore, BDNF signaling through TrkB receptors is likely to be involved in TCA patterning. The factors mediating the retrograde influence of NMDAR and mGluR5 signaling on TCA patterning remain to be elucidated.

Layer IV neurons form barrel rings and develop a polarized dendritic morphology

The barrel cytoarchitecture consists of distinctive cell-dense rings of layer IV neurons that project their dendrites towards the center of the cell-sparse barrel hollow where TCA arbors are situated (Woolsey *et al.*, 1975; Steffen & Van der Loos, 1980; Simons & Woolsey, 1984; Rice, 1985; Lubke *et al.*, 2000). The absence of barrel cytoarchitecture in Cx-NR1- and Cx-mGluR5-KO mice (Fig. 3) indicates a requirement for NMDAR and mGluR5 signaling in cortical excitatory neurons in orchestrating the lateral placement of layer IV neurons as they form barrel rings (Iwasato *et al.*, 2000; Ballester-Rosado *et al.*, 2010). In both mutant mouse lines, the dendritic polarity of layer IV spiny stellate neurons is also reduced (Datwani *et al.*, 2002; Ballester-Rosado *et al.*, 2010). In addition, dendritic outgrowths are also perturbed in these mutant mice, with a higher segment number and increased total length. Taken together these results suggest that both NR1 and mGluR5 are required to guide layer IV neurons to form barrel rings and develop a polarized dendritic pattern.

The cell-autonomous role of NMDAR in dendritic patterning of layer IV cortical neurons is most elegantly demonstrated by Espinosa *et al.* (2009) using the MADM (mosaic analysis with double markers) method to generate NR2B mosaic mutant mice. Analyzing the dendritic morphology of NR2B-KO neurons surrounded by wildtype neurons, they found that even at the barrel wall NR2B-KO neurons failed to develop a polarized pattern (Espinosa *et al.*, 2009). Interestingly, Wijetunge *et al.* (2008) found that NR2B is reduced in mGluR5-KO S1. mGluR5 can regulate NR2B expression through the FMRP-mediated local dendritic translational machinery (Westmark & Malter, 2007; Edbauer *et al.*, 2010). NMDAR and mGluR5 interact through adaptor proteins (Fagni *et al.*, 2004) and reciprocally

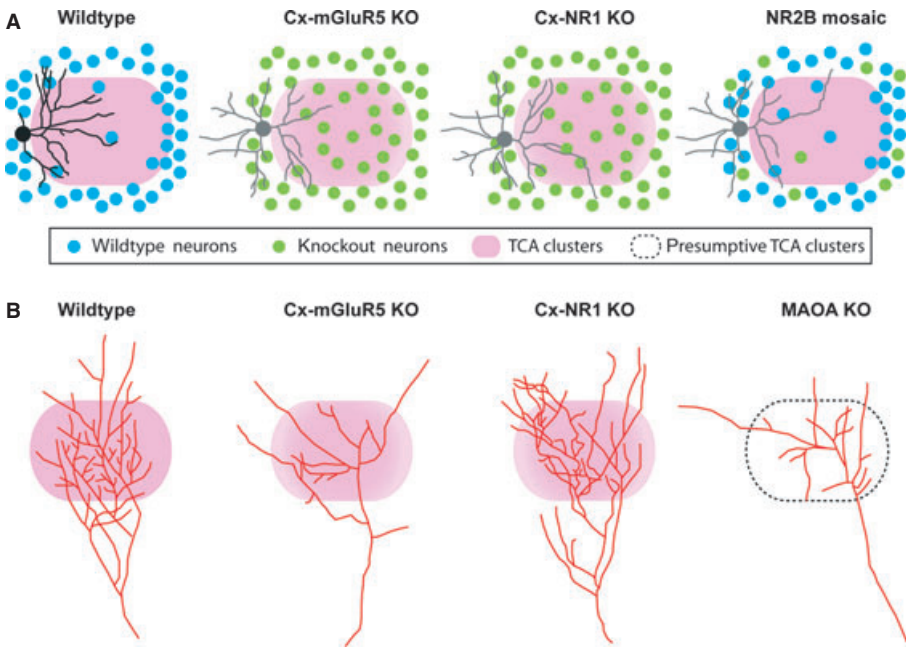

FIG. 3. Schematic diagram showing examples of reconstructed layer IV spiny stellate neurons and single thalamocortical axons in wildtype, Cx-mGluR5-KO, Cx-NR1-KO and NR2B mosaic mutant mice. (A) In wildtype mice, layer IV spiny stellate neurons show polarized dendritic morphology with the majority of their dendrites projecting toward the barrel hollow (pink). For simplicity, only spiny stellate neurons are depicted here. In both Cx-mGluR5- and Cx-NR1-KO mice, layer IV neurons are evenly distributed in the barrel field and have symmetric dendritic morphology (non-polarized pattern, depicted in grey). In NR2B mosaic-KO mice, mutant layer IV neurons located in the barrel walls show non-polarized dendritic pattern. (B) Examples of reconstructed single TCAs. In wildtype mice, the axon arbor in layer IV develops from a single axon, forming numerous axon collaterals, with a dominant orientation of the branches toward the barrel center; individual TCAs form highly branched and densely clustered arbors corresponding to the mapped facial whisker. In Cx-mGluR5-KO mice and MAOA-KO mice the complexity of TCA arbors is much reduced, and collaterals grow in divergent directions instead of forming a narrow cluster. In Cx-NR1-KO mice, TCAs have exuberant branches. Drawings are based on data shown in Datwani *et al.* (2002), Rebsam *et al.* (2002), Lee *et al.* (2005), Espinosa *et al.* (2009) and Ballester-Rosado *et al.* (2010).

modulate each other's function (Alagarsamy *et al.*, 2002, 2005; Heidinger *et al.*, 2002; Guo *et al.*, 2004). In addition, through a protein kinase C(PKC)–src pathway, mGluR5 activation leads to NR2B tyrosine phosphorylation (Guo *et al.*, 2004). Taken together, these results suggest that NR2B is likely to be regulated by mGluR5 activity in modulating dendritic patterning.

Postnatal apoptosis doesn't seem to have a major impact on barrel wall formation (Sanno *et al.*, 2010). In transgenic mice expressing a dominant-negative RhoA mutant in developing neurons, barrel cytoarchitecture develops normally despite a reduction in apoptosis and a significant increase in the number and density of cortical neurons.

Lesion-induced anatomical rearrangement in cortical whisker maps

The anatomical organization of both TCAs and cortical neurons will be dramatically rearranged if sensory input is disrupted by nerve damage within a few days of birth (Van der Loos & Woolsey, 1973; Killackey & Leshin, 1975; Woolsey & Wann, 1976; Simons & Land, 1987; Woolsey, 1990; Kossut, 1992). The developmental time window for triggering anatomical map plasticity ends around the time when the whisker-related pattern becomes obvious. However, delaying the appearance of the cortical whisker map by reducing the uptake of 5-HT with a 5-HTT blocker doesn't lead to alterations in the critical period of anatomical whisker map plasticity (Rebsam *et al.*, 2005). In addition, normal anatomical whisker map plasticity has been found in several mutant mice with whisker map deficits, including PKARIIβ (Inan *et al.*, 2006), Cx-NR1 (Iwasato *et al.*, 2000) and Cx-AC1 (Iwasato *et al.*, 2008). Taken together, these results suggest that the formation and the rearrangement of the whisker-related pattern in S1 use different mechanisms. Recently, Takasaki *et al.* (2008) found that, at young ages, the glutamate transporters GLT-1 and GLAST-1 are expressed mainly in astrocytes and are required for anatomical whisker map plasticity. Reduced anatomical rearrangements of TCAs triggered by electrocauterization of C-row hair follicles were found in both GLT-1- and GLAST-1-KO mice. This finding suggests that the regulation of ambient glutamate level in the extracellular space is critical for the anatomical rearrangements of TCAs and layer IV neurons. It remains an open question as to how the critical period of anatomical whisker map plasticity in the cortex is terminated prior to P4 and whether it is possible to extend the critical period for the anatomical rearrangement of thalamocortical connections.

The functional development of thalamocortical synapses

The preparation of the acute mouse thalamocortical brain slice described by Agmon & Connors (1991) allows one to preserve the neural circuits connecting the barreloids in the ventrobasal thalamus with the barrels in S1. This preparation has proven to be extremely valuable. A wealth of knowledge on the synaptic function and plasticity of thalamocortical synapses has been gained using various electrophysiological paradigms in conjunction with pharmacological reagents and transgenic mice in this slice preparation. Thalamocortical synapses are glutamatergic (White, 1978; Agmon & O'Dowd, 1992) and this neurotransmission is mediated through ionotropic glutamate receptors, including amino-3-hydroxyl-5-methyl-4-isoxazolepropi-creaseonate receptor (AMPAR), NMDAR and kainate receptors (Agmon & O'Dowd, 1992; Crair & Malenka, 1995; Kidd & Isaac, 1999). Below, we discuss the functional changes occurring in

thalamocortical synapses during the first two postnatal weeks when barrels are forming.

Maturation of thalamocortical synapses

Excitatory cortical layer IV principal neurons receive glutamatergic inputs from TCAs and neighboring glutamatergic neurons while receiving inhibitory inputs from cortical GABAergic interneurons (Agmon & Connors, 1991; Crair & Malenka, 1995; Petersen & Sakmann, 2000). The majority of interneurons connected to layer IV principal neurons receive direct inputs from TCAs (Porter *et al.*, 2001; Bruno & Simons, 2002; Inoue & Imoto, 2006; Sun *et al.*, 2006; Cruikshank *et al.*, 2007; Daw *et al.*, 2007a; Tan *et al.*, 2008). Thus, thalamic axons drive both excitatory and inhibitory cortical neurons, the latter triggering a fast feed-forward inhibition (Agmon & Connors, 1991; Beierlein *et al.*, 2002, 2003; Swadlow, 2003; Gabernet *et al.*, 2005) to limit the temporal window for integration and to sharpen the temporal resolution of thalamic inputs (Pinto *et al.*, 2000, 2003; Pouille & Scanziani, 2001; Wilent & Contreras, 2004).

Serial developmental changes in synaptic functions during the first two postnatal weeks, when barrels are forming, have been characterized (Fig. 2). First, AMPAR-mediated currents in thalamocortical synapses increase (Crair & Malenka, 1995; Barth & Malenka, 2001; Lu *et al.*, 2001). Second, the number of silent synapses (synapses containing only NMDARs) decreases with age (Isaac *et al.*, 1997). Third, the NMDAR subunit composition changes from NR2B-dominant to a mixed NR2A/2B NMDAR composition, accompanied by the shortening of NMDAR decay kinetics (Barth & Malenka, 2001; Lu *et al.*, 2001). The developmental increase in NR2A is likely to account for the acceleration of NMDA current kinetics in thalamocortical synapses (Lu *et al.*, 2001). Fourth, the feed-forward connections from TCAs to inhibitory neurons become strengthened toward the end of the first postnatal week (Daw *et al.*, 2007a). After the first postnatal week, thalamic stimulation often triggers a monosynaptic excitatory postsynaptic current immediately followed by an inhibitory postsynaptic current in both excitatory and inhibitory neurons (e.g. Fig. 3 in Porter *et al.*, 2001).

Thalamocortical synaptic plasticity

Synaptic plasticity in thalamocortical synapses can be induced with Hebbian-based pairing protocols (Daw *et al.*, 2007b; Inan & Crair, 2007; Fox, 2008). However, long-term potentiation (LTP; Crair & Malenka, 1995; Barth & Malenka, 2001; Lu *et al.*, 2001) or long-term depression (LTD; Feldman *et al.*, 1998; Lu *et al.*, 2003) can only be induced during the first postnatal week when barrels are forming. Thalamocortical LTP formation requires NR2B-containing NMDAR, calcium and PKA signaling (Crair & Malenka, 1995; Lu *et al.*, 2001, 2003). NMDAR is also required for LTD induction in rat thalamocortical synapses (Feldman *et al.*, 1998) but not in mice (H.C. Lu, unpublished observations). The temporal coincidence between the critical period for the synaptic plasticity of thalamocortical connections and the period of anatomical development of barrels is intriguing. This led to the hypothesis that Hebbian-based synaptic learning rules that adjust synaptic strength are the cellular mechanisms underlying cortical somatosensory map formation (Crair & Malenka, 1995).

Barrelless mice were the first mutant mice identified as lacking barrel cytoarchitecture (Van der Loos *et al.*, 1986; Welker *et al.*, 1996). The mutation in *barrelless* mice is a result of a loss-of-function in the calcium/calmodulin-stimulated AC1 (Abdel-Majid *et al.*, 1998). The robust cAMP synthesis triggered by calcium/calmodulin in wildtype cortices is greatly reduced in *barrelless* cortices (Abdel-Majid *et al.*, 1998). These findings imply that calcium influx triggered by neuronal activity may activate AC1 to increase cAMP concentration to instruct cortical map development. Detailed analysis of the functional properties of *barrelless* thalamocortical synapses found that *barrelless* synapses are stuck in an immature state with few functional AMPARs, but they are rarely silent (NMDAR-only; Lu *et al.*, 2003). Both LTP and LTD formation in thalamocortical synapses are difficult to induce in *barrelless* mice, probably due to an inability to properly regulate synaptic AMPAR trafficking. Despite these synaptic deficits, the developmental switch in NMDAR subunit composition occurs normally in *barrelless* mice.

PKA, the main target of cAMP, has been repeatedly implicated in synaptic plasticity (e.g. Gutlerner *et al.*, 2002; Lee *et al.*, 2003). PKARII β is expressed in the dendritic spines of cortical layer IV neurons when barrels are forming. In both PKARIIβ- and Cx-AC1-KO mice (Inan *et al.*, 2006; Iwasato *et al.*, 2008), thalamocortical LTP formation is defective and AMPAR-mediated current is reduced. These data support the role of the cAMP/PKA signaling in cortical layer IV neurons in regulating AMPAR trafficking upon LTP-like processes occurred during normal development. The reduced relative contribution of AMPA current to NMDA current in the thalamocortical synapses of NeuroD2-KO mice suggest that calcium-dependent transcription activity is likely to be involved as well (Ince-Dunn *et al.*, 2006). Taken together, the findings suggest that the developmental strengthening of AMPAR-mediated currents in thalamocortical synapses is regulated through calcium and cAMP/PKA signaling.

mGluR5, a group I mGluR, primarily activates Gαq, which stimulates phospholipase C to generate the second messengers IP3 and diacylglycerol (DAG) by hydrolyzing phosphatidyl inositol bisphosphate (PIP2). These cumulative actions modulate various kinases, ion channels and IP3-gated intracellular calcium stores (reviewed in Luscher & Huber, 2010; Niswender & Conn, 2010). mGluR5 is predominantly present in postsynaptic dendrites and spines (Romano *et al.*, 1995; Takasaki *et al.*, 2008) and has a prominent role in synaptic plasticity at many synapses. Activation of mGluR5 triggers rapid protein synthesis through local dendritic translational machinery (Merlin *et al.*, 1998; Huber *et al.*, 2000; Raymond *et al.*, 2000; Karachot *et al.*, 2001; Vanderklish & Edelman, 2002). At thalamocortical synapses of mGluR5-KO mouse, LTD formation is enhanced while LTP is absent (She *et al.*, 2009). At these synapses NMDAR-mediated currents also decay faster than at wildtype thalamocortical synapses. Faster decay kinetics may lead to altered calcium influx, which may be insufficient for LTP but adequate for LTD induction. Interestingly, the developmental increase in AMPAR current occurs normally in mGluR5-KO thalamocortical synapses. mGluR5 signaling maybe dispensable for the developmental increase in AMPAR-mediated current.

Prior to the formation of barrels, a significant proportion of thalamocortical synapses are functionally silent (NMDAR-only) and they can be converted to functional synapses (AMPAR-containing synapses) by an LTP pairing paradigm (Isaac *et al.*, 1997). FMRP is an RNA-binding protein and acts as a negative regulator of protein translation (Penagarikano *et al.*, 2007; Garber *et al.*, 2008). In *Fmr1*-KO (null mutant for FMRP) mice, there is an increase in the number of silent synapses towards the end of the first postnatal week and the temporal window for thalamocortical LTP formation is shifted to later ages (Harlow *et al.*, 2010). Interestingly, *Fmr1*-KO mice don't have barrel map deficits or alterations in the critical period for anatomical barrel map plasticity. An increase in the number of silent synapses after the first postnatal week has also been described in the BDNF-null mutant mice (Itami *et al.*, 2003). Despite a delay in the appearance of

whisker map, both the whisker-related TCA pattern and the critical period of barrel map plasticity are normal in BDNF-KO mice (Itami *et al.*, 2000). Taken together, these findings suggest that the presence of silent synapses is associated with the time window of LTP formation. The normal critical period for lesion-induced anatomical barrel map plasticity in both *Frm1* and BDNF-KO mice suggests that the activity-dependent conversion of silent synapses to functional synapses may not account for the cellular mechanism underlying anatomical rearrangements of thalamocortical synapses.

The functional development of the glutamatergic release machinery in TCAs

Mature thalamocortical synapses have a very high probability of release (Pr) and often contain many release sites per axon (Gil *et al.*, 1999). As a result, the transmission of an individual TCA is very reliable and efficient. *In vivo* recordings in adult rat somatosensory cortex revealed that synaptic responses in barrel neurons adapt rapidly to repetitive facial whisker deflections. The robust short-term depression at thalamocortical synapses is the main contributor to this adaptation (Chung *et al.*, 2002). These specialized features of the TCA release machinery are thus critical for sensory function. Nicotine and 5-HT can modulate TCA release machinery. Exogenous application of nicotine enhances TCA glutamate release as observed by an increase in the amplitude of evoked postsynaptic current and in the degree of short-term depression triggered by paired stimuli (Gil *et al.*, 1999). In contrast, 5-HT treatment leads to a reduction in evoked excitatory response (Rhoades *et al.*, 1994) and reduced short-term depression (Laurent *et al.*, 2002). It is plausible that the disrupted neurotransmission caused by excess 5-HT in the MAOA- and 5-HTT-KO mice prevents whisker map formation by acting on 5-HT1B expressed on TCAs (Bennett-Clarke *et al.*, 1993).

In *barrelless* and *RIM1α* (Rab3-interacting molecule 1α)-KO thalamocortical synapses, the release efficiency from TCAs is reduced as indicated by the decrease in short-term depression and probability of release compared to control TCAs (Lu *et al.*, 2006). Despite dramatic alterations in the presynaptic function of *RIM1α*-KO TCAs, barrel map deficits found in these mutant mice are subtle and mainly localized to the postsynaptic part of thalamocortical synapses: the barrel cytoarchitecture formed by layer IV neurons. Normal short-term plasticity and release probabilities were found in the thalamocortical synapses of Cx-AC1-, PKARIIβ- and mGluR5-KO mice, all of which have defective LTP formation (Inan *et al.*, 2006; Iwasato *et al.*, 2008; She *et al.*, 2009). These findings suggest that alterations in synaptic plasticity do not result in deficiencies in the release machinery.

In summary, all the barrel mutant mice found with dendritic patterning deficits are also defective in synaptic plasticity (including Cx-AC1-, mGluR5- and PKARIIβ-KO mice). This strongly supports the hypothesis that Hebbian-based synaptic learning rules are the cellular mechanism underlying the establishment and refinement of thalamocortical connections. In contrast, TCAs in Cx-AC1-, PKARII β- and BDNF-KO mice form whisker-related clusters in S1 despite the absence of thalamocortical LTP formation (Itami *et al.*, 2000; Inan *et al.*, 2006; Iwasato *et al.*, 2008). These data argue strongly against the role of LTP-like mechanisms in instructing TCA segregation into whisker-related clusters.

Conclusion

The participants involved in cortical whisker map formation often play additional and important roles in the functional maturation of thalamocortical synapses and in synaptic plasticity in mature synapses from diverse brain areas. It remains to be determined whether they activate similar or different signaling cascades for anatomically precise development of thalamocortical circuits and for synaptic function and plasticity. In many developmental processes, the anatomical organization is determined soon after the appearance of a primordium. Indeed, the expression of many molecules required for barrel formation (e.g. AC1, NMDAR and mGluR5) can be detected as soon as embryonic neurons become postmitotic. Are these molecules needed from the beginning of their expression in the presumptive area for barrels? Do glutamate receptors in developing neurons respond to regulated neurotransmitter release or spontaneous release? What is the nature of the activity-dependent processes required for fine-tuning thalamocortical connections? Answering these questions will undoubtedly advance our knowledge of the development cortical circuits in sensory processing.

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Abbreviations

5-HT, serotonin; 5-HTT, 5-HT transporter; AC1, adenylyl cyclase I; AMPAR, amino-3-hydroxyl-5-methyl-4-isoxazolepropicreaseonate receptor; BDNF, brain-derived neurotrophic factor; BSTC, brain stem trigeminal nuclear complex; CTA, corticothalamic axon; Cx-, cortex-specific; E, embryonic day; FMRP, Fragile X mental retardation protein; IP3, inositol 1,4,5-trisphosphate; KO, knockout; LTD, long-term depression; LTP, long-term potentiation; MAOA, monoamine oxidase A; mGluR5, metabotropic glutamate receptor 5; NeuroD2, Neurogenic Differentiation 2; NMDAR, *N*-methyl-D-aspartate receptor; NR1, NMDAR subunit 1; NR2B, NMDAR subunit 2B; P, postnatal day; PKA, protein kinase A; PKARIIβ, PKA regulatory subunit IIβ; PLC, phospholipase C; PSPB, pallial-subpallial boundary; S1, primary somatosensory (cortex); TCA, thalamocortical afferent; TrkB, tyrosine kinase receptor type 2; VPM, ventral posteromedial nucleus of thalamus.

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