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Neural activity: sculptor of 'barrels' in the neocortex

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Abstract

A major portion of the primary somatosensory cortex of rodents is characterized by the discrete and patterned distribution of thalamocortical axons and layer IV granule cells ('barrels'), which correspond to the spatial distribution of whiskers and sinus hairs on the snout. In recent years several mutant mouse models began unveiling the cellular and molecular mechanisms by which these patterns emerge presynaptically and are reflected postsynaptically. Neural activity plays a crucial role in conferring presynaptic patterns to postsynaptic cells via neurotransmitter receptor-mediated intracellular signals. Here we review recent evidence that is finally opening the doors to understanding the cellular and molecular mechanisms of pattern formation in the neocortex.

Topographic maps of the sensory periphery, and patterning within these maps are characteristic features of primary sensory neocortical areas. In normal laboratory rodents, layer IV of the primary somatosensory (SI) cortex contains a body map proportionate to the sensory receptor density in the periphery. Within this cortical map, thalamocortical axon terminals (TCAs) from the ventroposteromedial nucleus (VPM) and layer IV granule cells form discrete modules ('barrels') that replicate the patterned array of whiskers and sinus hairs on the contralateral snout (Fig. 1). Since the coining of the term 'barrels'[1], lesion studies noted that when the sensory periphery is damaged during perinatal times, TCAs fail to develop their normal patterning. Consequently, layer IV granule cells do not form or maintain barrels as cytoarchitectonic modules[2–4]. Aberrant numbers of whiskers on the snout are also reflected by corresponding patterns in the SI barrel cortex[5]. Functional alterations in the barrel cortex of adult animals that have undergone whisker lesions or trimming have also been noted[6–8]. Several lines of evidence indicate that somatosensory periphery-related neural maps and patterns are conveyed by the afferents at each synaptic relay station[9–12]. However, the mechanisms by which TCAs develop patterns and how their postsynaptic partners detect them are not well understood. Recent observations from mutant mouse models have opened new venues for understanding the mechanisms of barrel differentiation[13,14] (Fig. 2).

Gene deletion studies and *in vitro* assays are now revealing the molecular signals that direct topographic thalamocortical connections. For example, absence of several transcription factors prevents the normal pattern of gene expression in the thalamus and pathfinding of TCAs (Refs 15–17). Similar results have been found for the guidance molecule, semaphorin 6A (Ref. 18). Although these mutations prevent the ability of TCAs to reach appropriate cortical regions, other classes of molecules are involved in thalamocortical mapping[13,14,19–21]. For example, *EphrinA5* knockout (KO) mice display both a distorted face map and distorted alignment of TCAs in this region, yet distinct barrel patterns are present[19]. Developing TCAs transiently express growth-associated phosphoprotein GAP43 (Ref. 20). In *Gap43* KO mice, thalamocortical topography is severely disrupted and aberrant

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patches formed by TCAs no longer reflect the spatial organization of whiskers and sinus hairs[21]. Several neurotransmitters have also been shown to affect barrel patterning. To date, research on transgenic mice lacking a particular gene or combination of genes suggests two gross subdivisions of neurotransmitter receptor activity that are crucial for normal barrel development: presynaptic serotonergic receptor activity and postsynaptic glutamatergic receptor activity (Fig. 3).

Serotonergic autoregulation of thalamocortical patterning

In the late 1980s whisker-specific patterning of serotonergic fibers was noted in the developing rodent barrel cortex[22,23]. Combined immunohistochemistry and labeling of TCAs with lipophilic tracers, revealed that TCAs form periphery-related patterns first, followed by serotonin (5-HT)-positive fiber patterns[24,25]. Initially, it was thought that 5-HT-positive raphecortical projections mimicked TCA patterns[22–27]. A more recent study revealed that these 5-HT patterns actually reflect TCAs rather than raphecortical terminals[28]. Intriguingly, developing TCAs transiently express 5-HT_{1B} receptor [29] and the serotonin transporter (SERT/5-HTT), and thalamic neurons express the genes encoding 5-HTT and the vesicular monoamine transporter (VMAT2)[28,30] (Fig. 3). Although thalamic neurons do not synthesize 5-HT, their axons in the barrel cortex take up exogenous 5-HT via 5-HTT (Ref. 28). Internalized 5-HT is then stored at the nerve terminals or transported back to VPM cell bodies. *In vitro* recordings from thalamocortical slices indicated that 5-HT has a presynaptic inhibitory effect on glutamatergic transmission between VPM axons and barrel cortex cells[31]. Thus, 5-HT signaling could act as a regulator of glutamatergic transmission during patterning of TCAs. Presently, the precise role of transient 5-HT uptake and transport by TCAs during the sensitive period for pattern formation is not known.

A series of elegant studies in mice with mutations that led to increased 5-HT levels or abolished 5-HTT or 5-HT_{1B} function now offer insights into mechanisms of axonal pattern formation in the barrel cortex[32–35]. Disruption of monoamine degradation enzyme, monoamine oxidase A (MAOA), either by genetic deletion or by pharmacological blockade led to a large increase in 5-HT, a permanent expansion of thalamocortical projection fields, disrupted segregation of TCAs, and lack of barrels as cytoarchitectonic entities[32,34]. These cortical deficits were seen even though subcortical patterns were normal. The disruption of TCA patterning was caused by elevated 5-HT levels, and not other amines, because the cortical defects in *MAOA* KO mice could be rescued by pharmacological blockade of 5-HT synthesis[32]. The same group recently showed that the deleterious effects of excess 5-HT were mediated via the 5-HT_{1B} receptors and not 5-HT uptake via 5-HTT (Ref. 35). Although barrel patterns appear normal in *5-HT_{1B}* KO mice, genetic removal of 5-HT_{1B} receptors in *MAOA* KO mice restores normal patterning of TCA terminals and near normal segregation of cortical barrels. Furthermore, *5-HTT* KO mice showed similar deficits to those of the *MAOA* KO mice indicating a crucial role for 5-HTT in regulating extracellular 5-HT levels. 5-HT_{1B} removal in *5-HTT* KO mice or in *MAOA/5-HTT* double KO mice also restored barrel patterning in the cortex. In conjunction with previous findings that removal of 5-HT results in shrinkage but near normal patterning of the barrels, these data indicate that TCAs autoregulate their glutamatergic transmission via presynaptic mechanisms using 5-HT that is present in their target field. Thus, 5-HT_{1B} receptors could act as a key switch in gating co-active, patterned inputs traveling through the thalamocortical pathway, ensuring that the activity levels are matched by the distribution of individual thalamocortical fiber terminals (Fig. 3). 5-HT involvement in cortical pattern formation is largely at the presynaptic level, and most of the deficits seen in postsynaptic elements are probably a reflection of pattern defects in their presynaptic inputs. However, the incomplete segregation of cortical barrels leaves open the possibility of a role for postsynaptic 5-HT receptors in cortical pattern formation[35].

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Glutamatergic neurotransmission and cortical patterning

N-methyl-D-aspartate receptors (NMDARs) are widely expressed along the developing whisker-barrel neuraxis, including all layers of the neocortex[36,37]. Early studies examining the role of activity during early postnatal development reported that blockade of action potentials, or NMDARs along either the trigeminal nerve or at the cortical level did not affect cortical patterning[38–40]. Subsequent experiments using pharmacological blockade, however, resulted in abnormalities in functional and morphological integrity of the barrels and related cortical columns[41,42]. The negative results obtained in the initial studies might be attributed to the timing and effectiveness of the drug applications in a system where patterns emerge at late fetal stages in the brainstem and are established shortly after birth in the neocortex[43,44]. Furthermore, morphological analyses were carried out using either acetylcholinesterase histochemistry (an enzyme transiently expressed by developing rat TCAs), or by cytochrome oxidase histochemistry, a ubiquitous marker for cortical barrel fields. In these studies, the distribution of layer IV granule cells and their dendritic orientation were not examined.

By contrast, targeted deletion of specific genes related to neural activity consistently showed defects in whisker-related patterning along the mouse somatosensory pathway. To date, several mutant mice have been described with deficits in axonal and/or cellular patterning. Many of these mutations involve aspects of glutamatergic synaptic communication via ionotropic and/or metabotropic receptors. Deletion of intracellular signaling molecules downstream from neural activity also show defects in barrel formation[45–47] allowing, for the first time, a molecular dissection of the signaling pathways involved in cortical pattern formation and plasticity.

NMDARs and barrel development and plasticity

A role for neural activity and NMDAR-mediated activity has been underscored in the vertebrate visual system, hippocampus and neocortex[7,48,49]. Furthermore, LTP and LTD in the developing barrel cortex require NMDAR activation[50].

The first convincing evidence that NMDARs are a key player in the development of patterned connections along the rodent somatosensory pathway came with the description of mice with complete deletion of the crucial subunit, NR1 of the NMDAR complex[51]. These mice had normal topographic axonal projections between the whiskerpad and the brainstem, but completely lacked barrelettes, that is, patterns within the whiskerfield map in the brainstem trigeminal complex (BSTC). Similar results were later reported for the *NR2B* subunit KO mice[52]. Because both mice are postnatally lethal, pattern formation at higher trigeminal centers could not be studied. Iwasato *et al.*[53] addressed this problem by ‘rescuing’the *NR1* KO mice by ectopic expression of a transgene of *NR1* splice variants. When high levels of *NR1* transgene were expressed along the somatosensory pathways in the *NR1* KO background, whisker-specific patterns were restored. By contrast, low levels of transgene expression in *NR1* KO background failed to restore patterns in the principal sensory nucleus of the trigeminal nerve, VPM, and the face region of the somatosensory cortex. In these mice, absence of cortical and thalamic patterns could be attributed to the lack of patterning in the principal sensory nucleus, which conveys whisker patterns to the upstream somatosensory centers. Therefore, such genetic manipulations could not directly assess the role of NMDARs at the cortical level.

Spatial precision of NMDAR deletion at the cortical level has been a major technical challenge. This technical hurdle was recently overcome[54] by generating region specific *NR1* KO mice using *crelox* gene excision under the control of the cortex-specific *Emx1* promoter. In these mice (*CxNR1* KO), the *NR1* gene was deleted in all *Emx1*-expressing excitatory

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cortical neurons (and in hippocampus and olfactory bulbs), but remained intact elsewhere in the brain. In *CxNR1* KO mice, whisker-specific patterns developed normally in the BSTC and thalamus. In the somatosensory cortex, TCAs formed rudimentary patches representing large whiskers. By contrast, layer IV granule cells failed to develop barrels, even in regions in which TCAs showed patterns. Thus, in the absence of NMDAR function, granule cells fail to detect any patterning of their presynaptic partners, and fail to organize into barrel modules.

These data further suggest that NMDAR activation is necessary for the normal maturation of a full complement of thalamocortical patterning in the somatosensory cortex. The presynaptic effect in *CxNR1* KO animals might be as a result of misregulation of an NMDAR-stimulated release of a retrograde signal because the loss of NMDAR expression is restricted to cortex. Furthermore, whereas presynaptic NMDARs have been identified in the hippocampus, NMDARs in the adult somatosensory cortex appear to be largely postsynaptic[55]. The rudimentary patterning of TCAs in *CxNR1* KO mice indicates that cortical NMDARs are not necessary for the gross patterning of TCAs. However, detailed analyses in *CxNR1* KO mice showed that GABAergic interneurons escaped the *NR1* deletion, because of their origin from the ganglionic eminence in which *Emx1* is not expressed[56,57]. Hence, patterning of TCAs could be attributed to NMDAR activation in these cells, which also participate in cortical barrels[58,59].

Similar to normal mice, neonatal lesions of a row of whiskers on the contralateral snout of *CxNR1* KO mice resulted in fusion of the thalamocortical terminals representing the lesioned row of whiskers[54]. This finding appears to contradict an earlier report in which lesion-induced plasticity was prevented by APV infusion over the barrel cortex[40]. A notable possibility in explaining plasticity of TCAs in the *CxNR1* KO mice is the residual NMDAR function in GABAergic cells; a possibility that awaits further experimental analyses.

Metabotropic glutamate receptor 5 and barrel formation

Group1 metabotropic glutamate receptors ($mglu_1$ and $mglu_5$) have been implicated in hippocampal and cortical plasticity[60]. Furthermore, they are present along the developing somatosensory pathway during the sensitive period[61–63]. These receptors activate intracellular messenger pathways, positively regulating phospholipase C (PLC) and adenylyl cyclase (Adcy). Mice with deletion of the *Mglu*$_5$ receptor gene display segregation of large whisker TCAs into rows but not individual patches within rows, and lack barrels[45]. The complete loss of barrels, in spite of partial segregation of thalamic axons, indicates that $mglu_5$ receptor signaling is also crucial for the normal transfer of patterns from TCAs to their postsynaptic partners during barrel development. Interestingly, TCAs are segregated into a primordial barrel pattern as they traverse the cortical plate, before reaching layer IV (Ref. 12). It is not known whether the $mglu_5$ receptor is necessary for the initial segregation of TCAs or whether it is necessary for the maintenance of segregation in layer IV.

The deletion of the gene encoding the $mglu_5$ receptor was not restricted to cortex[64]; thus, the defect in thalamocortical axon patterning might be caused by incomplete barreloid formation in VPM and/or improper afferent signaling. There is evidence for a presynaptic mglu receptor in cortex that couples to PLC signaling pathways[65], although the precise mglu receptor subtype is not known. However, in adult animals, ultrastructural localization of $mglu_5$ indicates postsynaptic localization[63]. If it is the case that the locus of the defect in *Mglu*$_5$ KO mice is postsynaptic, retrograde signal(s) activated via $mglu_5$ and NMDAR signaling might be crucial for the maintenance of thalamocortical patterning. Furthermore, the differences in the defects in the TCAs in these two animals suggest multiple retrograde molecules might be necessary.

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Intracellular pathways

An understanding of the intracellular mechanisms by which receptor activity leads to altered structural and functional changes requires a dissection of the second messenger systems activated following receptor stimulation (Fig. 3). Several mutations in genes downstream from serotonergic and glutamatergic pathways in mice revealed phenotypes with disrupted thalamocortical or barrel patterning.

In 1996, a spontaneous mutation was reported, in which TCAs failed to pattern and no barrels formed[66]. These 'barrelless' mice exhibited normal laminar and topographic distribution of TCAs, but the overall thalamocortical projection field was larger, similar to that seen in *MAOA* KO mice (see Fig. 2). The mutation in the barrelless mice has been identified as mutation of the *Adcy* type I gene[67]. The gene product is a membrane-bound enzyme that catalyses the formation of cAMP and subsequently regulates the activity of the cAMP-dependent protein kinase A (PKA) and cyclic nucleotide-gated ion channels[68]. Because the 5-HT_{1B} receptor negatively couples to Adcy activity, these findings suggest that cAMP-dependent pathways regulate thalamocortical glutamatergic transmission and synaptic refinement, but additional postsynaptic defects cannot be excluded[67]. Several postsynaptic receptors, including $mglu_5$ receptors, also regulate Adcy activity. Indeed, differential effects on cortical neurons might explain functional differences in the barrel cortex of *Adcy1* KO and *MAOA* KO mice[69]. Indeed, deletion of the RIIβ isoform of PKA results in a near complete loss of cortical barrels, in spite of TCA segregation in the posterior medial barrel subfield (P. Neumann, pers. comm.). Therefore, the loss of TCA segregation in the *Adcy1* KO mice is not solely mediated by PKA. Furthermore, the dramatic effects on cortical segregation strongly suggest a postsynaptic role for PKA in barrel formation, possibly as a downstream target of cAMP generated following mglu activation or via NMDA activation of calmodulin[70].

Mice lacking the gene encoding phospholipase C-β1 (PLC-β1) also exhibit defects in barrel formation without affecting patterning of TCAs (Ref. 45) (Fig. 2). PLC-β1 is a G-protein-activated phosphodiesterase that hydrolyses phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2] into two second messengers: inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol (DAG). Ins(1,4,5)P_3 regulates intracellular $Ca^2{}_+$ levels by causing its release from the endoplasmic reticulum, and DAG controls the level of phosphorylating agent protein kinase C (PKC). The expression of PLC-β1 in the developing cortex is largely postsynaptic[71], and phosphoinositide hydrolysis following activation of the group 1 mglu receptors is dependent on PLC-β1 expression during the first postnatal[45] week β1 is indicating that $mglu_5$ receptor activation of PLC-crucial for barrel formation (Fig. 3). However, whereas the cortical deficits observed in *Mglu₅* KO mice appear to be mediated through receptor activation of PLC-β1, the effects on thalamic afferent segregation in *Mglu₅* KO mice must be mediated by another pathway, possibly via activation of Adcy1.

Ultrastructural localization of PLC-β1 gave insight into a possible cellular locus for the defects manifested in these knockout mice. PLC-β1 is concentrated in intermediate-compartment-like organelles called 'botrysomes', which are found within and near dendritic roots[72,73]. Apart from their more traditional roles in intracellular signaling (see above) PtdIns(4,5) P_2, Ins(1,4,5)P_3 and DAG have all been shown to play a role in vesicular trafficking. Thus, PLC-β1 activation might regulate protein trafficking into dendrites in response to synaptic activity during dendritic differentiation, perhaps by regulating the release of neurotrophins because preproBDNF can be purified from the botrysome (Fig. 3)[72]. The primary locus of the postsynaptic neuronal defect in *CxNR1*, *$Mglu_5$*, *PkarIIβ* and *PLC-β1* KO mice is unknown. Three distinct, yet potentially overlapping, possibilities exist: (1) dendrites fail to develop, remaining in a relatively immature state; (2) dendrites develop,

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but are unable to respond to cues from TCAs and fail to reorient into the barrel hollows and (3) cortical neurons are unable to migrate to the barrel walls. Our preliminary evidence from *PLC-β1* and *CxNR1* KOs suggests that dendrites do develop a relatively normal level of complexity, indicating that they might be unable to organize around incoming TCAs.

Postsynaptic pathways involved in transfer of patterns from TCAs to barrel cells

Do the defects in the *CxNR1* and *Mglu*$_5$ KO mice reflect distinct cellular mechanisms, both necessary, but insufficient for cortical differentiation? Or, do these receptors activate overlapping intracellular pathways and similar downstream effector molecules? Recent isolation and characterization of a postsynaptic NMDA receptor complex, or 'Hebbosome', suggests that NMDARs and group 1 mglu receptors might be acting via overlapping, or synergistic mechanisms[74,75]. This 2000 kDa multiprotein complex contains at least 77 proteins, 49 of which participate in NMDAR signaling. The component proteins fall into five main categories: (1) NMDARs and mglu receptors (but not the AMPA receptors), (2) adaptor proteins, (3) protein kinases and phosphatases, (4) cytoskeletal proteins, and (5) cell adhesion proteins. Both PKARIIβ (Ref. 74) and PLC-β1 (S.G.N. Grant and H. Husi, pers. commun.) are components of the Hebbosome, further supporting a role for this multiprotein complex in cortical differentiation. A striking feature of the composition of the Hebbosome is that there appears to be 'modules' or sets of signaling proteins that are known to comprise key components of signal transduction pathways. This raises the possibility of dissecting distinct pathways within the Hebbosome that underlie barrel formation. The points of potential cross-talk between NMDAR and mglu$_5$ receptor signaling in the developing barrel cortex are not known, however, there are several candidate Hebbosome constituents including mitogen-activated protein kinase (MAPK), which can be activated by both PKA and PKC (Ref. 76), and calmodulin-dependent protein kinase (CAMK). A point mutation in the *Camk2α* gene (*α-Cam Kinase II*) that abolishes autophosphorylation prevents physiological plasticity in the barrel cortex of juvenile and adult animals[77]. Furthermore, CAMK, MAPK and PKA can activate transcription factors including cAMP response element-binding protein (CREB), which has been implicated in adult barrel plasticity[78,79]. Taken together these findings suggest that Hebbosomes integrate signals arising from different patterns of activity and then instruct the subsequent intracellular changes.

Concluding remarks

It has been a little over thirty years since the coining of the term 'barrels'by Woolsey and Van de Loos[1]. Hendrik Van der Loos envisioned that the key to understanding barrel cortex development and plasticity lies in the analysis of genetic alterations. To this end, he and his colleagues bred numerous mice expecting to obtain spontaneous mutations that would help us understand how the barrel cortex organization is matched to the sensory periphery[5]. The 'barrelless' mice emerged in the colony established by them, a few years after the untimely passing away of Van der Loos. Present-day mouse molecular genetics and transgenic and knockout strategies are now expediting this vision, unveiling the molecular and cellular mechanisms of sensory map formation, patterning and plasticity in the mammalian brain.

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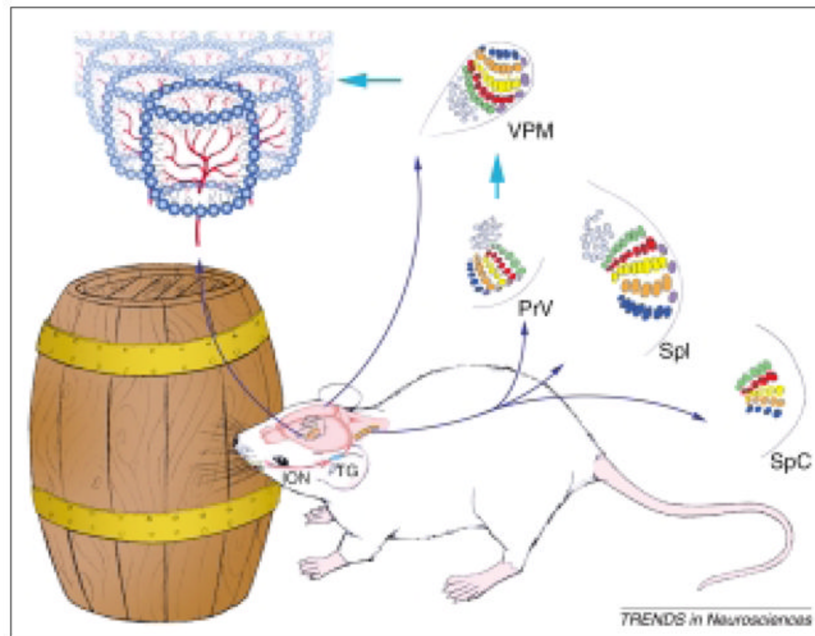

Fig. 1.

The whisker-barrel pathway of mice. The infraorbital (ION) branch of the trigeminal ganglion (TG) innervates the whiskerpad on the snout. Central counterparts of these axons deliver the patterns to the brainstem trigeminal complex, where whisker-related patches are called ‘barrelettes’.

Abbreviations: PrV, principal sensory nucleus of the trigeminal nerve; SpI, SpC, subnuclei interpolaris and caudalis of the spinal trigeminal nucleus. Barrelette neurons of the PrV carry these patterns to the ventroposteromedial nucleus (VPM) of the contralateral dorsal thalamus. In VPM, whisker-related patterns are referred to as ‘barreloids’. Barreloid or VPM neurons form the final relay to the layer IV somatosensory, ‘barrel’ cortex. At each level there is a topographically aligned map of the face (and the body) and whisker-specific patterning of axonal and cellular elements within the face map. In mice, a mature cortical barrel consists of a cell-dense barrel wall with asymmetrically projecting dendrites oriented into cell-sparse barrel hollows where incoming thalamocortical axon terminals (TCAs) segregate. These patterns are established during a sensitive period in development under the guidance of signals coming from the sensory periphery[1–4].

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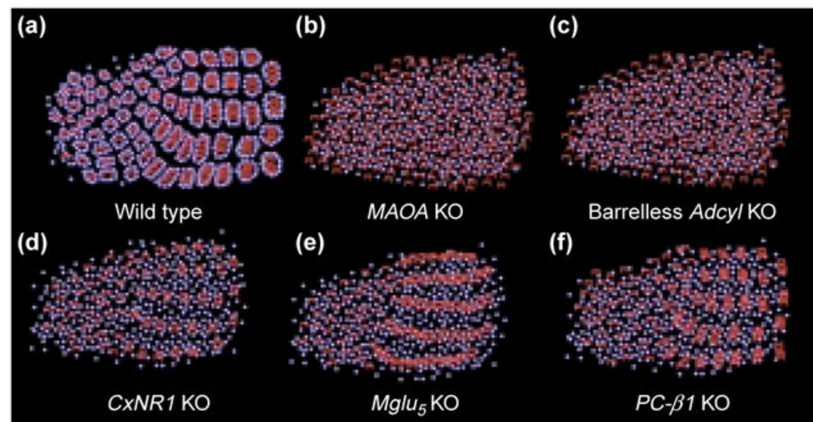

Fig. 2.

Thalamocortical axon terminals (TCAs) and barrel defects of several mutants discussed in this review. Barrel cells are depicted as blue spheres and TCAs as red arbors. In wild-type mice, TCAs form discrete patches and the distribution of these patches reflects the patterned array of whisker and sinus hair follicles on the contralateral snout. Layer IV granule cells organize around these patches forming the 'barrels'. In *Maoa* and *Adcyl* knockout (KO) mice TCA distribution is not patterned and there are no barrels. In *CxNR1* KO mice the TCAs representing the large whiskers mainly form rudimentary patches, but there are no barrels, even in this region of TCA patterning. In $mglu_5$ KO mice, TCAs form continuous bands corresponding to five rows of whiskers, and there are no patches or barrels. In *PLC-β1* KO mice, TCAs form whisker-specific patches but there are no barrels.

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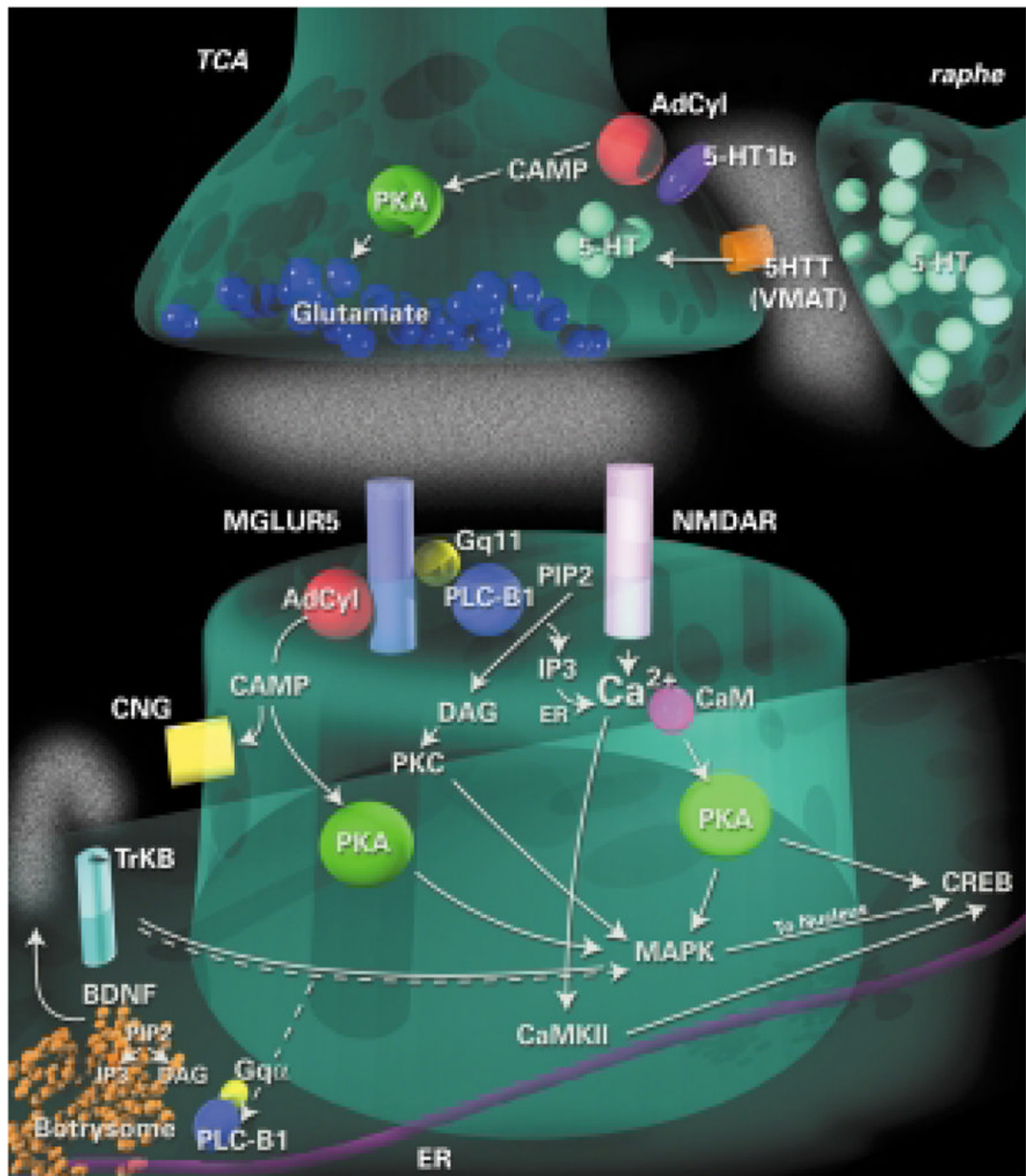

Fig. 3.

Putative intracellular signaling pathways involved in barrel differentiation. Research on transgenic mice suggests two gross subdivisions of neurotransmitter systems that are crucial for normal barrel development: presynaptic serotonergic receptor activity and postsynaptic glutamatergic receptor activity. Furthermore, the intracellular pathways downstream of these receptors are beginning to be elucidated. Abbreviations: AdCyl, adenylyl cyclase; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}–calmodulin kinase type II; CREB, cAMP response element binding protein; DAG, diacylglycerol; IP3, inositol (1,4,5)-trisphospate; MAPK, mitogen-activated protein kinase; MGLUR5; metabotropic glutamate receptor 5; NMDAR, NMDA receptor; PIP2, phosphatidylinositol (4,5)-bisphosphate; PKA, protein

kinase A; PKC, protein kinase C; PLC-B1, phospholipase C β1; TCA, thalamocortical axon terminals; VMAT, vesicular monoamine transporter.

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