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Neuronal plasticity and regeneration in the olfactory system of mammals: morphological and functional recovery following olfactory bulb deafferentation

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Abstract. The mammalian olfactory system has the unique property in the permanent turnover of the olfactory sensory neurons under normal conditions and following injury. This implies that the topographical map of the epithelium-to-bulb connections generated during ontogenesis has to be maintained despite neuron renewal in order to insure olfactory information processing. One way to investigate this issue has been to disrupt the peripheral connections and analyze how neural connections may be reestablished as well as how animals may perform in olfactory-mediated tasks. This review surveys the main data pertaining to both morphological and functional recoveries taking place in the peripheral olfactory system following olfactory bulb deafferentation. Conclusions from these studies are enlightened by recent data from molecular biology.

Key words. Olfaction; nerve transection; bulbectomy; regeneration; behavioral recovery; topographical map; odor coding.

Introduction

The mammalian olfactory system has the remarkable capacity to discriminate among a wide range of odor molecules. This begins with the olfactory receptor neurons that form a sensory epithelium within the posterior part of the nasal cavity. They are the only neurons that make direct physical contact with the environment. This contact occurs on specialized cilia that project from the sensory neuron dendrites into the mucus covering the olfactory epithelium. The cilia-specific localization of G-protein-coupled odorant receptors (ORs) is consistent with a possible role of ORs in olfactory signal transduction [1]. Olfactory receptor neurons also send unbranched, unmyelinated axons centrally to the olfactory bulb. The bulb is the first relay in the olfactory pathway, where axons of primary olfactory neurons form synapses with the dendrites of second-order neurons (mitral cells and tufted cells) and interneurons (periglomerular cells) within structures called glomeruli. Second-order neurons, which are modulated by local intrabulbar circuitry, integrate the input from olfactory sensory neurons.

A unique feature of the mammalian olfactory epithelium is its ability to turn over: olfactory sensory neurons, which have a life-span ranging from 30 to 120 days, are replenished continuously throughout life [2, see 3 for review]. The turnover is supported by a population of neuronal precursor cells located in the basal region of the neuroepithelium. It has been largely demonstrated that neurogenesis in the olfactory epithelium is greatly enhanced following olfactory nerve injury or chemical exposure, thus allowing a rapid reconstitution of the damaged epithelium and reestablishment of functional connections with second-order neurons in the deafferented olfactory bulb [4]. This regenerative capacity of olfactory neurons may have special relevance for the maintenance of olfactory function that is known to play a critical role for animal survival. Overall, a constant readiness for anatomical adjustments has to be maintained in the olfactory system, so that any reorganization must manage to preserve normal function.

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Most of the studies on the functional organization of the olfactory bulb have been focused on obtaining evidence for spatial activity patterns in response to odor stimuli, and searching for the anatomical epithelial-bulb connections underlying these patterns [for review, see 5 and 6]. There is a consensus that the topographical ordering in the projection from the olfactory epithelium to the bulb is modest compared with the point-to-point projection described in other sensory systems, which suggests that topographical ordering of odor properties might be sharpened at the bulbar level. Recent data from in situ studies indicate that primary olfactory neurons expressing a specific odorant receptor project to only a few topographically fixed glomeruli so as to create specific odor maps, which serve as the basis for odor quality discrimination [7–9]. We do not yet know what exactly the olfactory bulb maps, but understanding the topographical organization seems to be a necessary starting point for assessing mechanisms of olfactory processing. This it particularly relevant since the topographical map must be maintained in adult animals despite the turnover of the olfactory receptor neurons.

Understanding the peripheral organization of the olfactory system requires knowledge of the logic underlying the connections between first-order neurons and the second-order ones. One way to investigate this question is to disrupt these connections and analyze the effects from the molecular to the behavioral level. Even though olfactory receptor neurons have the ability to regenerate and reinnervate the olfactory bulb after deafferentation, it is not yet fully proven that the pattern of reinnervation replicates the original pattern of axonal innervation. This review surveys the major work pertaining to relationships between functional recovery and olfactory nerve reinnervation following injury of the peripheral olfactory pathway in mammals. We will review data from injury obtained either by ablation of the olfactory bulb (bulbectomy) or by olfactory nerve transection (axotomy): both induce selective degeneration of the olfactory sensory neurons. Conclusions from these studies will be enlightened by recent advances in molecular biology.

Neuron degeneration and recovery in the olfactory epithelium following olfactory nerve transection and bulbectomy

Regulation of neuronal death and neurogenesis

It has been demonstrated that experimental injury to the olfactory nerves by using nerve transection at the cribriform plate or olfactory bulb removal induces rapid and massive death of mature olfactory receptor neurons [10–14], as well as of a small percentage of immature neurons and globose basal cells [15–16]. Olfactory neurons die through a well-established apoptosis program, and fragmentation of nuclear DNA, which is a hallmark of apoptosis, reaches a peak between 1 and 2 days post-injury [15, 17]. This massive neuronal degeneration, which occurs during the first 5 days post-lesion, finds expression in a dramatic reduction (50–70%) in the thickness of the olfactory epithelium. Within the same time, an increased proliferation of neuronal precursor cells is observed in the basal compartment of the neuroepithelium [see 3 for review, 18]. The proliferative response, which reaches a peak by 5 days post-lesion, results in the replacement of many of the lost neurons.

Differences in the reconstitution of the olfactory epithelium have been observed according to the presence or the absence of the synaptic target, the olfactory bulb. Restoration of the olfactory epithelium after axotomy is consistently better than after bulbectomy, with recovery to near control values after 30 days post-lesion [13]. By contrast, even at long intervals following a unilateral bulbectomy (1–9 months), the reconstituted olfactory epithelium has not fully regained the thickness of the control side [12, 19–21]. In addition, the olfactory epithelium on the lesioned side remains in a relatively immature state, since mature neurons, which are immunoreactive for the olfactory marker protein (OMP) and carnosine, appear greatly reduced in number [19, 20, 22], whereas immature neurons expressing the growth-associated protein (GAP)-43 predominate [19, 21]. Several studies have shown that the reconstituted epithelium exhibits an upregulation of neuron precursor proliferation that is accompanied by an increase in the rate of cell death [21, 23, 24]. In absence of the target tissue, the life span of newly generated neurons is noticeably shortened, on the order of 10 days or less [21, 24], thus suggesting a trophic dependence of olfactory neurons upon the olfactory bulb for their prolonged survival. Factors regulating neurogenesis and programmed cell death in the olfactory epithelium have been reviewed elsewhere [25].

Regulation of olfactory receptor expression

The size of the OR gene family has been estimated to be 500–1000 genes in mammals, which means that each OR gene should be expressed by only 0.1–1% of the primary olfactory neurons [see 26 for review]. Thus, each neuron expresses one or only a few OR genes. Analysis of the spatial pattern of OR expression in the rodent olfactory epithelium reveals that neurons expressing a given OR are confined to one of three to four broad rostro-caudal epithelial zones, where they are randomly interspersed with neurons expressing other ORs [27–29]. The distribution of OR types in typical zonal patterns has been observed before the onset of synaptogenesis in the olfactory bulb, which indicates that OR gene expression and zonal patterning are intrinsic properties of the olfactory epithelium [30, 31].

The zonal patterning of OR genes in the epithelial sheet actually remains almost without any physiological correlate. In an attempt to shed some light on this issue, we have studied, in adult mice, the effects of olfactory bulb removal upon the expression of various OR genes in the reconstituted epithelium [32]. Following unilateral bulbectomy, the expression of three OR genes (OR5, OR14, OR124), each being present in a different epithelial zone, has been analyzed at different intervals following the surgery. We have noted that the number of olfactory neurons expressing a given OR decreases in the olfactory epithelium on the lesioned side to reach a minimum of about 30% of the control value at 5 days post-bulbectomy. This decay of OR-expressing cells appears in line with the massive decrease in the number of mature neurons reported after both olfactory nerve transection and bulbectomy. An almost complete abolition of OR gene expression has also been observed in the olfactory epithelium of chicken embryos 2 days following a unilateral olfactory nerve transection [33]. A progressive recovery of OR expression in mice primary olfactory neurons takes place and reaches a plateau at day 15 post-lesion. Newly formed neurons expressing a given OR are located in their specific epithelial zone of expression, which confirms the intrinsic expression of OR genes, even in adult animals. However, differences in OR recovery are reported according to their zonal patterning. Whereas OR124 expressed in the lateral zone reaches 70% of the control value after 35 days post-bulbectomy, OR14 expressed in the dorsal zone remains at 35% of the control value. This may reflect some specific features probably not related to regional morphological or physiological differences, but rather to differential effects of the lack of olfactory bulb. This assumption has been confirmed by axotomy experiments in which no zonal difference is observed in the OR reexpression which is achieved by 15 days following the nerve transection [32]. This suggests that neurons in a specific zone such as the dorsal zone may be more dependent on trophic influence from the bulbar target. As emphasized previously, since olfactory neurons are trophically dependent on the presence of the bulb for a prolonged survival, our results give some insight on possible zone-specific parameters that may govern the life span of olfactory neurons.

Reinnervation and functional recovery following bulbectomy

Morphological recovery

Following complete removal of the olfactory bulb in adult rats and mice, the newly formed olfactory receptor neurons send their axons through the cribriform plate, but they terminate in large neuromas and do not make contact with the brain [22, 34, 35]. Olfactory nerve penetration appears to be blocked by the formation of scar tissue in the cavity previously occupied by the olfactory bulb. A recent study has shown that nonneuronal cells in the scar completely surround regenerating axon bundles and exhibit robust expression of semaphorin III, which is a chemorepellent protein [36]. It has been proposed that probably in addition to growth-inhibitory molecules, semaphorin III secreted by cells in the scar generates a chemorepulsive barrier in the bulbar cavity that prevents extension of regenerating olfactory axons. By contrast, ablation of the olfactory bulb in neonatal rodents results in marked forward displacement of the frontal lobe, which protrudes into the space vacated by the bulbectomy [35, 37]. In these conditions, olfactory receptor neurons are capable of innervating the ipsilateral spared forebrain by forming glomerulus-like structures in the host tissue [34, 35, 37]. Olfactory nerve penetration into the forebrain subsequent to bulb removal is an age-dependent process, since from postnatal day 13 in rats, this penetration is blocked by glial scar tissue [38].

Partial ablation of the olfactory bulb also induces structural rearrangement of the bulbar tissue and then changes in the organized connections. In cases of small lesions, the bulb remnant maintains its normal morphology. However, the regrowing olfactory axons that are deprived of their specific target, are not preferentially attracted by the glomerular layer remaining, but form ectopic glomerular structures in any layer of the bulb remnant [39, 40]. The ectopic glomeruli are seen to affect the direction of the neighboring mitral cell dendrites that often reorient towards the newly formed neuropiles. The apical dendrites of mitral cells profusely branch within neuropiles and make synaptic contacts with olfactory axon terminals [40]. In cases of large lesions (more than 50% of the bulb), large areas of the remnant bulbar tissue lost their typical layered organization, since regrowing axons form glomeruli at random into these areas [40]. As for small lesions, these glomeruli appear connected to the apical dendrites of spared mitral cells, which present a variety of unconventional orientations to branch with them.

Functional recovery

It has been demonstrated that unilateral bulbectomy has little or no effect on various measures of odor sensitivity or discrimination in adults rats [35, 41]. By contrast, bilaterally bulbectomized animals exhibit impairment in their olfactory ability in simple retrieval of hidden food that can be considered as a highly conserved basic task [35].

Following partial lesions of the two olfactory bulbs, adult rats retain the ability to detect a variety of odors [42–45]. Slotnick et al. [44] relate studies in which adult rats are first trained to various odor-conditioning tasks and then received lesions that remove the medial or the lateral surface of the rostral part of the olfactory bulbs. Lesioning of the medial surface of the bulb removes a discrete group

of glomeruli known for exhibiting high levels of metabolic activity in 2-deoxyglucose-treated rats exposed to propionic acid. Data show that animals present no deficit in absolute detection of propionic acid, neither in intensity difference thresholds nor in ability to discriminate propionic acid from novel odors. Based on the same experimental paradigm, rats have received unilateral bulbectomy and removal of different parts of the contralateral bulb [45]. It has been demonstrated that animals with relatively small remnants of one bulb can still perform odor detection and discrimination. But some rats with less than 21% of their glomeruli saving present more random responses; animals make many errors and/or fail on some of the detection or discrimination tasks. On the other hand, partial bulbectomy of the two bulbs in newborn pups does not seem to induce alteration of olfactory-guided behavior. For example, no deficit on nipple attachment and consequent suckling, which depend on the presence of olfactory cues on or near the nipple, have been reported in 8-day-old rats following destruction of different areas of the bulb [46]. As well, after medial or lateral removal of up to 80% of the olfactory bulbs, newborn rabbits are still able to respond to the pheromone-governing suckling behavior and continue to respond appropriately to artificial odors learned prior to lesioning [47].

Taken together, these data indicate that a relatively small remnant of olfactory bulb, which may be about 20%, could provide a sufficient anatomical substrate for detection of a variety of odors and for odor discrimination. This confirms that the olfactory system, which is essential to animal survival, is provided with a high degree of redundancy. The combined pattern of convergence and divergence reported in the connections between the epithelium and the bulb [48–50] might underlie the dispersion of information processing by conferring redundancy on input to local regions of the bulb [51]. The fact that information encoding odor quality should be distributed among the remaining glomeruli agrees for a multiple, but not holographic, representation of the odor. Thus, a significant part of the olfactory information, which means sufficient to the reconstruction of the odor representation, might be found in each bulbar territory, but not necessarily the same everywhere. Such redundancy also implies that there may be more than one glomerulus with a particular input pattern. This seems to be the case since it has been reported that ORs in the mouse olfactory epithelium usually project onto few glomeruli that are detected on both the medial side and the lateral side of each bulb [7, 9, 52], which suggests that each olfactory bulb represents two symmetrical sensory maps of odorant receptors.

Lessons from bulbectomy experiments may be clarified by recent data from molecular biology. Shipley and Ennis [6] have hypothesized that a given OR should not be specific to an odor, but rather is relatively specific for a ligand, that is a specific molecular recognition site that may be present on many different odorant molecules. Thus, each odor molecule might have several potential recognition sites. This assumption has been recently confirmed by Malnic et al. [53] who use calcium imaging and single reverse transcriptase-polymerase chain reaction (RT-PCR) to demonstrate that a single OR can recognize multiple odorants. Conversely, a single odorant can be recognized by multiple ORs, but different odorants should be recognized by different a combinations of ORs. This model is based on a combinational receptor coding scheme used to encode odor identity and to discriminate odors, a given OR possibly recognizing a given structural feature of the odorant among others [53, see fig. 8]. These results are reinforced by a recent study of unitary extracellular recordings in the rat olfactory epithelium showing that olfactory receptor neurons are broadly responsive to qualitatively distinct odor molecules [54]. A broad tuning of olfactory sensory neurons has also been reported in previous single-unit studies in amphibians [55]. On the basis that the code for an odor consists of a combination of ORs, it could be inferred that any change in perception of an odorant quality might be the result of changes in its receptor code [53]. Thus, one can assume that olfactory bulbs presenting a reduced number of glomeruli, as reported following partial bulbectomy, might be capable of distinguishing among a wide range of odor quality so long as odors have receptor codes represented in the remaining olfactory neurons and glomeruli. It should be of interest to verify if animals with only few remaining glomeruli would be anosmic to many odors.

Reinnervation and functional recovery following olfactory nerve transection

Morphological recovery

Morphological studies have demonstrated that following olfactory nerve transection, axons of the new olfactory sensory neurons are capable of reinnervating the deafferented glomeruli. The time course of recovery has been well studied, and there is a large consensus that olfactory axons from newly formed sensory neurons reach the glomerular layer within 20–35 days after nerve transection in rodents [10, 56–59]. As shown by electron microscopy [56] and by anterograde horseradish peroxidase (HRP) transport [58], the first synaptic contacts between the olfactory axons and the dendrites of second-order bulbar neurons are observed in the same time range. With longer recovery times, 60 and 120 days post-axotomy, more substantial amounts of regenerating axons are observed in the olfactory nerve layer of the bulb [59]. At the bulbar level, it has been reported that 126 days following axotomy in aging hamster, new axons are not always confined to the glomerular layer; some are also seen penetrating the

different layers of the olfactory bulb to form small ectopic glomeruli along their pathway [58].

It has been suggested that the successful axon reinnervation of the deafferented olfactory bulb after axotomy is related to the growth-permissive properties of the olfactory ensheathing cells present in the olfactory nerve layer of the bulb [57, see 60 for review]. These glial cells produce a variety of molecules, including cell adhesion and extracellular matrix proteins as well as growth factors that support neurite outgrowth. Interestingly, these ensheathing cells, which remain intact after axotomy but are removed by bulbectomy, have the ability to penetrate glial scar tissue, enabling regenerative sprouts to pass through the non-permissive lesion site [61].

Functional recovery

Behavioral studies indicate that there is restoration of olfactory-mediated behavior following reinnervation of the olfactory bulb [59, 62, 63]. A direct correlation has been established between the time course of behavioral recovery for both odor detection and odor discrimination tasks and the amount of regenerating axons present in the bulb [59]. In a delay of 19–25 days corresponding to the onset of reinnervation of glomeruli, bilaterally axotomized hamsters become again capable to detect and discriminate between odors, and their performance steadily returns to preoperative levels within a period of 40 days. The authors report, however, that the time course of behavioral recovery is similar to that obtained preoperatively during the initial training period. Since animals were tested throughout the postoperative recovery period and received food reinforcement, it has been suggested that restoration of sensory function following axotomy may not be the reacquisition of a learned stimulus response but rather the relearning of a stimulus during the process of bulbar reinnervation. This hypothesis has been verified in hamsters that were first trained to discriminate between two odors before bilateral axotomy and then tested only from the 40th day post-surgery [63]. On days 40 and 43, animals were tested without food reinforcement to determine whether they can discriminate between the two previously learned odors and from day 46, reinforcement was again introduced. Data show that hamsters have to be retrained to discriminate between odors, even familiar ones, before they can reacquire the ability to perform an odor discrimination task. This suggests that odor quality perception changes after recovery and that the ability to discriminate between previously learned odors requires the additional training or relearning to bring performance back to control levels [63].

One can ask if changes in odor perception reported following olfactory nerve transection might be related to some rearrangement in the projection patterns between the epithelium and the bulb during the reinnervation process. We have actually few insights on this issue, and they refer to studies performed in genetically altered strains of mice in which olfactory sensory neurons expressing the OMP gene or the P2 receptor gene could be visualized using X-gal staining. The pattern of bulb reinnervation following induced lesion in the olfactory epithelium with Triton X-100 has been analyzed in H-OMP-lacZ-6 transgenic mice [64]. In this line of transgenic mice, lacZ expression is limited to a subset of olfactory sensory neurons located in a discrete band of neuroepithelium and projecting to a few glomeruli in the ventromedial region of the olfactory bulb [65, 66]. After 6–7 weeks of recovery, the pattern of X-gal staining in the reinnervated olfactory bulb accurately reflects that seen in untreated animals, which argues that newly formed neurons project onto the original ventromedial region of the bulb [64]. The question remains whether regenerating axons converge back to the same glomeruli in order to recreate the initial topographical map generated during ontogeny. Some insight is given by use of the P2-IRES-tau-lacZ transgenic mice in which neurons expressing the P2 receptor project to only two topographically fixed loci in the olfactory bulb [9]. It has been reported that 2–4 months following unilateral nerve transection, some of the regenerated P2-expressing axons can still converge. Although P2 axons show convergence onto discrete loci, they do not converge to the normal P2 glomeruli, thus demonstrating that following axotomy, new olfactory axon connections do not restore the original P2 map [67]. It seems that topographical maps probably serving as a basis for odor quality discrimination are altered after recovery from nerve transection. Indeed, Costanzo's experiments demonstrate that P2 receptor convergence does not require a specific glomerulus located in a fixed position in the olfactory bulb, but as a consequence, restoration of function requires additional odor training. The author concludes that complete recovery or the return of normal odor sensation may require restoration of the original odor maps.

With regard to axon reconnection following olfactory nerve transection as well as to olfactory neuron renewal, the proposal of Mombaerts [26] on a 'sniff-out' guidance function for OR is attractive. Since neurons first choose an OR gene for expression and their axons then find their bulbar target, it could be speculated that the OR itself may be an instructive determinant in the guidance process that maintains or reestablishes the functional connections between the olfactory epithelium and the bulb [9]. Data from experiments on knockout mice, in which the coding sequence of the P2 olfactory receptor is removed, indicate that the axons expressing the knocked-out receptor project to the bulb normally [68]. Once on the bulb, the axons do not converge on specific glomeruli but rather appear to wander broadly in the outer part of the olfactory nerve layer. Furthermore, receptor substitu-

tions that replace the coding region of one receptor gene with that of another uniformly alter the pattern of convergence [9, 68]. From this, it has been proposed that selection of the precise glomerular targets should require both the olfactory receptor and additional guidance receptors that may reflect the epithelial zone in which the OR is expressed [68]. The function of OR might be to initiate intracellular signaling events that lead to the expression of distinct axon guidance molecules or alternatively, to insure expression of molecular markers that guide growing axons of a particular type to their appropriate bulbar target [26, 68, see 69 for review]. Among specific carbohydrates that may be involved in olfactory targeting, it has been proposed that OCAM, an axonal surface glycoprotein expressed by subsets of axons in a zone-specific manner, may play an important role in selective fasciculation and zone-to-zone projections of the primary olfactory axons [70]. The question remains, when olfactory axons reach the bulb, what factors attract processes to specific glomeruli or repel them from incorrect target regions? One easy way to resolve the question should be to bring into evidence at the bulbar level counterreceptors (ORs and/or guidance molecules) that are expressed on the dendrites of mitral/tufted cells or interneurons. Lines of evidence indicate that the establishment of topographic maps does not depend on direct cues provided by the major synaptic targets of the sensory neurons in the olfactory bulb. Genetic crosses between P2-IRES-tau-lacZ mice and mutant mice lacking either interneurons or second-order neurons exhibit a convergence of P2 axons to glomeruli at positions analogous to those reported in wild-type mice [71]. Future research will certainly focus on identifiying attractive or repulsive guidance signals that allow olfactory axons to reach their final destination in specific glomeruli.

Conclusion

From a molecular biology standpoint, there is general agreement for the presence of a topographical map in the bulb with the location of the glomeruli for a given OR fixed in a species. The formation of this map seems to be hardwired and genetically programmed, which implies that the question of wiring in the olfactory system should be relocated at the bulbar level in order to determine how recognition between axons of first-order neurons and dendrites of second-order neurons is accomplished. Otherwise, since a given olfactory neuron differs from the others by the receptor it expresses and its axonal projection to the bulb, it may be assumed that processing of olfactory information should occur in the olfactory bulb and higher brain structures. One function of the glomerulus might be to shape the response of the output neurons so that they are more sharply tuned to a given odor than are the olfactory neurons conveying inputs to the glomerulus [see 72 for review]. Thus, it may be that activation of specific areas of the olfactory bulb is not necessarily a critical component of the olfactory code; it may be that local interactions and relative activity levels across the bulb are more informative than absolute levels at specific sites [73]. Together with the fact that olfactory coding involves spatial and temporal representations of the odor, both cooperatively contributing to higher processing, this clearly suggests that knowledge of the neuronal organization of the olfactory bulb is far more complex that was believed and may indicate directions for future study.

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