that the problem is a multidisciplinary one, relating chemistry, biology, and psychology. The field of olfaction has recently entered the medical clinic, a testimony both to the human significance of this sense modality and to the level of sophistication of present knowledge about it.

With more sophisticated research the relationship between subjective odor experience of humans and objective odor-guided behavior of animals has become clearer, and is an indication of the development of scientific understanding. According to the present multi-author review, this development can be summarized under four main headings: the olfactory stimulus, its transduction into a neural response, the neuroscience of the olfactory system, and the plasticity of the perception and behavior elicited by olfactory stimuli.

Finally, Gesteland presents the conclusion, and it is a timely statement about the present state of the science of smell as revealed in present topical reviews augmented by his own broadly based research ranging from biochemistry to psychophysics.

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Ontogeny of the olfactory code

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Key words. Olfaction; olfactory bulb; olfactory epithelium; odor-guided behavior development.

In altricial species, such as the rat, olfactory system development is precocious compared to other sensory systems and its function is necessary for early postnatal survival. Apart from its importance in the control of early behaviors, the developing olfactory system has a number of features that are of more general interest to chemosensory scientists and developmental neurobiologists. In mammals, the synaptic mechanisms of the olfactory bulb undergo considerable postnatal modifications. Understanding the ontogeny of the bulb provides information about the maturation of interneuronal pathways, the biological basis of early learning, as well as the neural substrate that is necessary for, at least, the rudimentary olfactory capabilities exhibited by the newborn pup. The olfactory bulb has afferent connections with a number of structures in the basal forebrain and receives efferents from several of its projection areas as well as from important cholinergic, noradrenergic, and serotonergic systems. With its simplified morphology, the bulb presents a useful model system for studying the factors that control the formation of neuronal connections within the brain and the effects of neurotransmitter systems on these processes.

The maturation of olfactory receptor neurons involves very different processes and follows a very different time course from that of the olfactory bulb. In the rat, a substantial portion of receptor cells exhibit mature properties at birth. As in other vertebrate species, these neurons have an apparent lifespan of 30-60 days and thus are constantly being replaced and undergoing differentiation in animals of all ages. For the physiologist, the turnover of receptor cells raises two fundamental issues. First, how does an organism achieve perceptual constancy with the unending turnover of synaptic inputs driving second order neurons. Second, how do the properties of receptors change as they differentiate and how might these differences bias experiments that attempt to describe the nature of the olfactory code among those (mature) neurons that are synaptically connected to the brain.

This paper will focus broadly on the developmental plasticity of olfactory neurons. In interest of coherence, it will concentrate on experiments related to the rat, a species for which the ontogeny of olfaction has been described in anatomical, physiological, and behavioral studies.

The ontogeny of odor-guided behavior

Suckling is the most conspicuous behavior exhibited by the newborn rat pup. During the first postnatal week pups depend on olfactory cues to locate their mothers' nipples. When suckling is measured on anesthesized dams, alterations in thermal (cooling the mother) or tactile (shaving the mother) cues have small effects on nipple attachment. In contrast washing the nipples to eliminate olfactory cues abolishes suckling in 3–4-day-old pups and reapplication of an extract of the nipple wash or pup saliva re-establishes this behavior[5].

Recent experiments have also provided evidence that neonatal rats can be conditioned to approach or avoid a novel odor. Rudy and Cheatle[68] paired novel odors with illness-inducing injections of lithium chloride in 2-day-old rats and subsequently demonstrated aversions to the odor six days later. Similarly, Martin and Alberts[53] have paired odors with the occurrence of illness or exposure to a cold temperature and shown conditioned changes in cardiac response rate. Other investigations have demonstrated olfactory learning in newborn rats by pairing exposure to an odor with a positive appetitive reinforcement. Johanson and Teicher[36] demonstrated that deprived 3-day-old pups can learn to approach a novel odor that has previously been paired with the delivery of milk through an intraoral cannula. Johanson and Hall[35] used a similar appetitive conditioning task and showed that performance depends on several variables known to affect conditioning in adults (stimulus-reinforcement contingency, deprivational state, use of the same stimulus for conditioning and testing). The demonstrations that suckling is mediated by olfactory cues and that odor aversions and preferences can be conditioned in neonatal pups indicate that nasal chemosensory systems are functional and capable of learning at this early stage of ontogeny. At present, there are no data indicating whether the main or accessory (vomeronasal) olfactory systems mediate these responses and thus their neural substrate is uncertain. However, as there is little known about the physiology of the developing vomeronasal system, this paper will focus on the functional maturation of the main olfactory system.

If rat pups exhibit conditioned aversions and preferences for odors, then it is possible that learning plays a role in the mediation of suckling by olfactory cues in the newborn. Blass and his colleagues have approached this issue by analyzing the exteroceptive stimuli which control the rat pup's first nipple attachments. Teicher and Blass[78] used the anesthesized dam preparation[5] to demonstrate that a rat pup's first nipple attachment is impaired by washing the mother's nipple to remove olfactory cues. Subsequently, painting the nipples with wash extract, mother's saliva, or amniotic fluid significantly increased the percentage of pups completing their first attachment. Painting the nipples with other olfactory stimuli (including mother's urine and virgin female saliva) did not stimulate initial attachments. Pedersen and Blass[58] tested the role of learning in this process by adding citral (a lemon scent) to the amniotic sac (prenatal exposure) and then placing newborn pups in a citral scented nest and stroking them with a brush for one hour (postnatal exposure). In subsequent testing, treated pups attached to nipples in the presence of citral but not in clean air, even when the dams nipples were unwashed (to which untreated pups attached). Pedersen, Williams, and Blass[59] used an analogous procedure to study odor conditioning in 3-day-old pups. Pups exposed to citral and simultaneously activated by either stroking with a brush or injecting d-amphetamine exhibited subsequent suckling in the presence of citral. In contrast, pups exposed to citral without activation, exposed to citral following activation by caffeine, or pups stroked or activated with amphetamine, without exposure to citral exhibited no such behavior. Further, training with citral did not generalize to testing with benzaldehyde (an almond-like odor) and training with benzaldehyde did not generalize to testing with citral. The effectiveness of activation by amphetamine but not by caffeine points a finger at catecholamine-containing neurons as possible mediators of this early form of conditioning. This possibility is underscored by the evidence (reviewed below) that the noradrenergic innervation of the olfactory bulb is remarkably precocious.

Taken together, the literature provides clear evidence that neonatal rats depend on olfactory cues to mediate suckling behavior, odor preferences and aversions can be conditioned in 2 or 3-day-old pups, and the association of an odor with some forms of stimulation (stroking with a brush, amphetamine) can elicit subsequent suckling behavior in the presence of that odor. There are two major limitations to apparent odor learning capabilities of neonatal rats. First, they are task dependent. Other investigators have shown that olfactory control over behaviors such as huddling or home-nest orientation are not apparent until the second postnatal week[1,22]. The task dependancy is also demonstrated by the observation that mere exposure to an odorant in the presence of tactile stimulation (without any stimulus response contingency) is sufficient to condition suckling to the presence of that odorant. Given its behavioral limitations, it may be more reasonable to consider this early olfactory conditioning as a form of imprinting rather than an example of early associational learning.

Second, unlike ingestive behavior in the adult, suckling in the neonate is not regulated by internal signals related to satiety. Hall and Rosenblatt[23] studied the effects of intraoral food loads on suckling behavior and reported that rats younger than 15 days of age continued to suckle and receive milk even after delivery of food loads large enough to cause refluxes up the esophagus. Similarly, Cramer and Blass[8] provided pups with a series of anesthesized, milk replete dams (using oxytocin to induce milk let-down) and found that 5 and 10-day-old pups will consume inappropriately large volumes of milk, while 15 and 20-day-old pups successfully regulated intake. Unlike, satiety, food-deprivation can increase the rate at which pups consume milk although it is not clear that this reflects a specific response to privation or a generalized increase in behavioral activity which is also associated with food deprivation in neonatal rat pups[5,79].

Developmental differences among olfactory receptor cells

The mature olfactory epithelium contains several types of cells with nuclei located in a pseudostratified arrangement. Receptor cells are bipolar neurons with cell bodies staggered throughout the middle third of the epithelium and an unbranched dendrite with a terminal end, the olfactory vessicle and cilia, lying in the mucus layer. Sustentacular cells are shaped like columnar epithelial cells. These have a cylindrical distal portion, cell bodies located closer to the epithelial surface than those of the receptors, a midsection that is compressed by the band of receptor cell nuclei, and proximal branches which end in contact with the basal cells. Basal cells, which lie between the basal lamina and the proximal ends of sustentacular cells, have a high rate of mitotic activity and have been

implicated as the stem cells for the replacement of receptor neurons[21,56].

The maturation of olfactory receptor neurons is marked by fundamental alterations in morphology, biochemistry, and physiology. Nevertheless, by the time of birth, the olfactory epithelia of rats and mice contain some receptor cells which appear to be mature. In mice, the olfactory placode is distinguishable by the tenth day of gestation (E-10) and primordial axons sprout and grow into the olfactory bulb by E-11[9,10,27,28]. By E-12, receptor cell axons have penetrated deep into the olfactory bulb and formed synapses with second order neurons[27,28]. Within the next several days, the olfactory receptor cells of the fetal mouse exhibit several other signs of maturity. Around E-14, these neurons begin to express the olfactory marker protein, a substance synthesized by the receptor cell that is unique to the primary olfactory pathway[15]. About this same time, there is an increase in the number and an elongation of cilia on the dendritic knobs of the receptor neurons[10]. Similarly, the olfactory epithelium contains Bowman's glands and exhibits signs of histochemical maturity by E-17[9].

Although published data are limited, receptor neurons in the fetal rat appear to follow a developmental pattern similar to that of the mouse with a lag of several days. According to Farbman and Margolis[15] olfactory marker protein is first expressed on day E-18 in the rat and E-14 in the mouse. Similarly, receptor cell axons of the rat arrive at the bulb on day E-16 and form synapses with second order neurons on E-18[18].

In the rat, the stages of physiological development parallel the changes in morphology and chemistry of the maturing fetal olfactory receptors. Electrophysiological studies of mammalian receptor neurons have been limited by the difficulty of obtaining reliable recordings in adult animals. Perhaps as a result, there have been no systematic studies of the response properties of receptor neurons in rats more than 30 days old and none in mice of any age. Gesteland and Sigwart[17] first succeeded in making in vitro recordings of receptors in tissue excised from postnatal rats and maintained under high oxygen tension in a specially designed chamber. They reported that these neurons have response properties similar to those described other species (primarily frogs) for which data has been published. When presented with stimuli of increasing concentration, the summated receptor potential (the electro-olfactogram or EOG) increased monotonically (fig. 1). Recordings of extracellular action potentials in this preparation showed that individual neurons respond selectively to stimulation with different odorous substances and that these odorant-evoked responses change in a complex, yet consistent, fashion as stimulus concentration is varied (fig. 1). At weak concentrations, neural activity increases for the duration of the stimulus event. With stronger stimuli, evoked responses consist of an intense initial burst of action potentials followed by a period of diminished activity. At the highest stimulus intensities, neurons driven by odorants tend to respond with a single, short latency burst of activity which was followed by a prolonged quiet period. These concentration-dependent response patterns are consistent with reports of single unit activity in the olfactory epithelia of non-mammalian vertebrates[16,33].

Gesteland et al.[18,19] studied the electrophysiological properties of the olfactory epithelium in rat fetuses. Like, Gesteland and Sigwart[17] they used an in vitro preparation in which tissue was excised and rapidly placed in a chamber having a high oxygen tension and they succeeded in obtaining reliable recordings for up to 7 h. Recordings of EOG activity were obtained as early as day E-14, a time at which olfactory receptors are distinguishable although they are not connected synaptically to the brain and they have not yet expressed the olfactory marker protein[15]. These early EOG recordings are like those in more mature rats and in other vertebrate species. In particular, they exhibit similar waveforms, there is a monotonic relationship between stimulus concentration and the amplitude of the negative wave of the EOG, response magnitude decreases as the electrode is driven deeper into the epithelium, and the responses to adaptation are similar[18]. Single unit responses were recorded as early as day E-16. Although stimulus concentration was not manipulated systematically for many neurons, response patterns were observed for different cells which were consistent with the concentration dependent response patterns described by Gesteland and Sigwart[17] for the postnatal rat. The most dramatic change noted for the developing fetal receptor cells involved response specificity. On the earliest days studied (E-17 to E-20) the receptor cells were driven by most substances used as stimuli, with neurons responding to an average of 85–98% of odorants on a given day. Just prior to birth (day E-21) there was a sudden increase in response selectivity, with neurons responding to an average of 54% of stimulus substances.

The analysis of maturational processes in the olfactory receptor cell must be tempered by the realization that complete data do not exist for any single species. Nevertheless, it appears that the formation of synapses in the olfactory bulb is a pivotal time in the life cycle of the olfactory receptor cells of fetal rodents. Within days of this event, there is a burst of maturational activity within

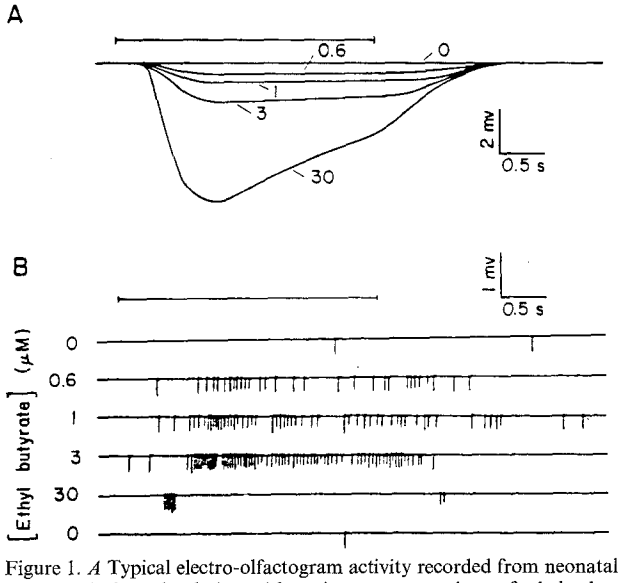

Figure 1. *A* Typical electro-olfactogram activity recorded from neonatal rat pups during stimulation with various concentrations of ethyl n-butyrate. *B* Typical responses of receptor neurons during stimulation with the same odorant in a similar preparation. Concentrations are in micromoles/liter air. Reprinted with permission from Gesteland and Sigwart[17].

the receptor cell dendrite and its ciliary appendages (mice), olfactory marker protein is first expressed and seems to be localized in the most mature neurons (mice, rats) and there is an abrupt transition in the selectivity of neural responses (rats). There is other evidence that receptor cells in the regenerating epithelium of the frog undergo a similarly sudden transition at about the time that their axons reinnervate the olfactory bulb. The olfactory epithelium of the frog contains some neurons which bear short motile cilia and others with much longer, immotile cilia[34,49]. Mair et al.[49] have presented evidence that the motility of the cilia is dependent on the properties of the cell to which they are attached and that the immotility of the longer cilia cannot simply be ascribed to the inertia associated with their length. Following ablation of the olfactory epithelium of the frog by ZnSO4, new receptor neurons are produced and gradually reinnervate the nose and there is an orderly transition from an epithelium containing sparse motile olfactory cilia (two weeks after treatment) to an epithelium covered with motile cilia containing sparse immotile cilia (four weeks after treatment) to an epithelium containing a mix of motile and immotile cilia (6 weeks after treatment). The first appearance of immotile cilia occurs at about the time that receptor axons reinnervate the olfactory bulb[49,76]. Based on these data, Mair et al.[49] have argued that the lifespan of receptor neurons in the frog can be divided into two stages. During the initial stages of development, they bear motile cilia and are involved in the removal of odorous molecules from the olfactory epithelium. When they mature, they bear long immotile cilia (which provide a larger surface area for transduction processes), are in synaptic contact with (and thus provide olfactory information to) the central nervous system, and they function as discriminating receptors.

Perhaps the most intriguing aspect of the constant turnover of olfactory receptor neurons is the ability of animals to achieve perceptual constancy. There is good evidence for a number of species of an ability to make consistent responses to a given odorant over periods of time that rival (and even surpass) the apparent lifespan of the receptor neuron. If this is the case, then the olfactory system must be able to produce a consistent response to a given odorant even though most, if not all, receptor neurons have been replaced and the newly formed cells have made synaptic contacts within the olfactory bulb. There are at least two general ways in which constancy could be accomplished: anterograde and retrograde specification. In the case of anterograde specification, receptor cells are inherently tuned to respond to certain stimuli and perceptual constancy is achieved by receptor cell axons being able to find their way to connect with the appropriate mitral cell. In the alternative of retrograde specification, specificity resides in the mitral cells and receptors are tuned to respond to specific stimuli by the mitral cell with which they happen to synapse. Although neither hypothesis can be disproven by the evidence that exists today, the data seem most consistent with the retrograde hypothesis. If mitral cells control the response properties of the receptors with which they synapse, then developing receptors would be expected to exhibit an abrupt change in response specificity after synaptogenesis similar to that described by Gesteland et al.[18,19]. Likewise, the abrupt transition in other properties of the receptor cells at about this same time is consistent with the idea that synapse formation with mitral cells has a fundamental impact on the maturation of these neurons.

Development of central olfactory mechanisms: morphology

Whereas the major events in the ontogeny of the receptor epithelium occur before birth, the olfactory bulb and the central olfactory pathways undergo considerable postnatal modification. Traditionally, the relay neurons of the olfactory bulb have been designated as mitral and tufted cells. Only a subgroup of tufted cells (primarily internal tufted cells) have processes the leave the olfactory bulb and these apparently have physiological properties similar to those of the mitral cells[20]. For these reasons, the discussion of relay neurons in this paper will be restricted to mitral cells. The bulb of the adult rat contains approximately 45000 ± 2000 mitral cells[31] each of which receives inputs from approximately 1000 receptor cells and has axonal processes which travel along the lateral olfactory tract and terminate in a number of structures in the basal forebrain collectively referred to as primary olfactory cortex. Primary olfactory cortex includes the anterior olfactory nucleus, pyriform cortex, olfactory tubercle, nucleus of the lateral olfactory tract, the anterior and posterolateral cortical amygdaloid nuclei and parts of the hippocampal rudiment and entorhinal cortex[6,11,63,64,75]. For each mitral cell, the olfactory bulb contains something on the order of 100 interneurons. Most of these are granule cells, small axonless neurons which form reciprocal dendrodritic synapses with mitral cells and receive dendritic inputs from mitral cell collaterals, other types of bulb interneurons, and from axons arising in other parts of the brain[60–62,65]. Apart from granule cells, there is at least one other class of interneuron, the periglomerular cells, which synapses with mitral cells and there are several other types of short-axon interneurons which synapse onto granule and periglomerular cells but have no direct connections with the relay neurons that transmit olfactory information from receptor neurons into other parts of the brain[60–62,69].

The development of neurons in the olfactory bulb has been studied most thoroughly in the mouse, primarily by J.W. Hinds and his colleagues. The results of these studies provide evidence that the afferent pathway from receptor neurons to primary olfactory cortex is developed prior to the maturation of interneuronal connections within the bulb. In the mouse, pulse labeling of dividing neurons with tritiated thymidine has demonstrated that most mitral cells are formed between the third and eleventh day of gestation (E-3 to E-11) whereas granule cells are produced primarily between E-18 and postnatal day 20 (P-20)[25,26]. Analogous results have been reported for the olfactory bulb of the rat[2–4].

Morphological observations provide other evidence of the early maturation of mitral cells. At the time of birth, light microscopic studies using Golgi methods have shown that mitral cells attain proper orientation with axons joining the lateral olfactory tract and dendritic processes forming characteristic tufts in the vicinity of receptor axon terminals in mice[27,32], rats[46] and opossum

pouch young[55]. At this same time, autoradiographic studies have shown that most granule cells have not been formed (in rats and mice)[1-3,25,26] and those that are present appear to be morphologically immature (in rats and opossum pouch young)[46,55]. In the rat, counts of cell bodies in Nissl stained material and analyses of morphology in Golgi stained material have demonstrated a dramatic increase in the number of interneurons, particularly those with a mature appearance, during the first two weeks of postnatal life[46]. By electron microscopic analysis of autoradiographic material, Kaplan and Hinds[37] have demonstrated that granule cells continue to be produced and added to the olfactory bulb in 3-month-old rats and they have calculated that the majority of granule cells in the bulb of a 24-month-old rat may have been produced after the animal was more than three months old.

Ultrastructural studies have provided a picture of synapse formation in the olfactory bulb of the mouse that closely parallels observations made at the light microscopic level. Presumptive receptor to mitral axonodendritic synapses first appear in the glomerular region of the bulb on embryonic day 15, about the time when mitral cell processes reorient and innervate this area[28-30]. The number of synapses in the glomerular layer peaks about the third postnatal week while the number of synapses in the external plexiform and granule cell layers, areas of dense granule cell synaptic activity, are still increasing after the sixth postnatal week[29]. Mitral and granule cells communicate through reciprocal dendrodendritic synapses. During the first postnatal week, the olfactory bulb of the mouse contains numerous unpaired mitral to granule (M/G) cell synapses, a few paired M/G and G/M synapses, and lacks unpaired G/M synapses[29,30]. Based on these data, Hinds and Hinds[29,30] have argued that newly differentiated granule cells form M/G synapses on outgrowing dendrites and only later form G/M synapses on processes that already bear a M/G synapse. If this is true, then the order in which the dendrodritic connections develop imposes an additional delay on the age at which granule cells first form synapses by which they can influence activity of mitral cells. The picture that arises from the literature is of an early maturation of the direct afferent pathway from the receptor epithelium to primary olfactory cortex that only later develops into the complex synaptic machinery characteristic of the mature olfactory bulb[72]. Such an arrangement might provide the bare bones of an afferent olfactory pathway at the time of birth that would presumably be capable of mediating primitive odor-guided behaviors.

Leonard[39] studied the development of bulb projections in the golden hamster by mapping patterns of degeneration argyrophilia following removal of a bulb in animals of varying ages. For newborn hamsters, she reported short lasting (24 h) degeneration throughout all mature bulb projection areas with the exception of entorhinal cortex and cortical amygdala. In contrast, longer lasting (72 h) degenerative changes, which Leonard has related to the existence of functional synapses, were limited to rostral areas of pyriform cortex. The early development of bulb projections have been verified in other species with different anatomical methods. Schwob and Price[71] injected tritiated leucine into the olfactory bulb of fetal and neonatal rat pups. Following injections on day E-17, label was distributed throughout the lateral olfactory tract and by E-19 was apparent in pyriform cortex. At birth, injections in the bulb produced labeling throughout all projection areas except for limited parts of the olfactory tubercle and lateral entorhinal cortex and transport patterns were similar to those in adults by day P-9[71]. Westrum[80] examined tissue from the pyriform cortex of newborn rats with electron microscopy and reported the appearance of numerous mature synapses presumably involving mitral cell axons at birth. According to Westrum, the number of synapses increases rapidly and neuropil develops such that the area resembles adult tissue by P-14. Similarly, Derer et al.[12] have reported the occurrence of axodendritic synapses, involving lateral olfactory tract fibers, as early as day E-15 or 16 in mouse embryos although they noted that the synapses seemed to be with dendrites of polymorphic cells which do not ordinarily form such synapses in adult tissue.

Taken together, the data provide evidence that primary olfactory cortex of rodents is remarkably precocious and forms functional connections with mitral cells at the time of birth although it is by no means certain that functional connections are formed in all bulb projection areas at this time. In a recent series of experiments, M. T. Shipley and his colleagues have used horseradish peroxidase – wheat-germ agglutinate to trace the afferent and efferent connections of the olfactory bulb in the rat pup. When injections are made on the day after birth, anterograde transport of label is apparent in the normal adult projection areas of the bulb with the exception of the olfactory tubercle, which is partially innervated[74]. More striking developmental differences are apparent among the efferent pathways from the brain to the bulb. On the second postnatal day (P-2), there are weak or non-existant efferent fibers from structures such as the anterior olfactory nucleus or the nucleus of the lateral olfactory tract that form substantial reciprocal connections with the bulb in more mature animals. In contrast, there are much more robust projections to the bulb from nonolfactory nuclei, including the locus coeruleus, the nucleus of the diagonal band of Broca, and the dorsal raphe nucleus[70,74]; structures associated, respectively, with norepinephrine, acetyl choline, and serotonin containing neurons. The early development of locus coeruleus projection is supported by evidence that the olfactory bulb of the rat contains 225 pmoles of NE/gm tissue at birth, an amount that increases to 500 pmoles at two weeks and 700 pmoles at three weeks of age (F. Margolis, personal communication, 1983). On the other hand, histochemical analyses have shown that the bulb contains no acetyl choline esterase or choline acetyltransferase until two weeks after birth, and this evidence has led Ooteghem, Schmacher, and Shipley[57] to argue that cholinergic mechanisms are immature in neonatal rat pups.

The precocious development of NE projections from locus coeruleus to the olfactory bulb is striking in view of evidence that brain catecholamines are critically involved in the formation of odor memories in young rats. As mentioned above, exposure of a non-suckling pup to an odorant following an injection of d-amphetamine can condition a subsequent suckling response during the presentation of that odorant[59]. Marcuso et al.[52] have reported that depletion of brain catecholamines by 6-hy-

droxydopamine (6-OHDA) treatment impairs the ability of newborn rat pups to form preferences for conspecific odors. Similarly, Cornwell-Jones et al.[7] have shown that neonatal rats treated with 6-OHDA persist in exhibiting odor preferences conditioned prior to 6-OHDA treatment that are normally altered by experience. Although the data do not distinguish between NE and dopamine (DA), there are several arguments against dopamine being critically involved in the effects of amphetamine or 6-OHDA treatments on the activity of olfactory neurons in newborn rat pups. First, the olfactory bulb receives very limited extrinsic dopaminergic inputs and although it contains intrinsic dopaminergic neurons there is evidence that these are not as precocious as other DA containing cells in the brain. Specht et al.[77] mapped the activity of tyrosine hydroxylase (an enzyme required for DA synthesis) and reported that it is not expressed in the olfactory bulb until the day before birth (E-21), a week after its appearance in cell bodies in the brainstem and diencephalon. Second, the olfactory tubercle, the one area of primary olfactory cortex with a dense DA input[14], is one of the last to receive fibers from the bulb[39,71,74].

The olfactory bulb can be viewed as a system under the control of feedback loops of increasing complexity[11,66]. At the simpliest level, there are interneuronal pathways within the bulb by which mitral cells can interact in a relatively direct manner. At a more complex level, several of the projection areas of the olfactory bulb contain neurons with axons terminating back in the bulb which, presumably, modulate mitral cell activity based on the activity of primary olfactory cortex. At a still more complex level, the bulb receives inputs from structures such as the locus coeruleus, nucleus of the diagonal band of Broca, and the dorsal raphe nucleus which do not have direct olfactory projections and presumably have functions related to other aspects of internal state condition. It appears that the newborn pup lacks the feedback loops which mediate neuronal interactions at the level of the olfactory bulb or the primary olfactory cortex. The precocity of the noradrenergic, cholinergic, and serotonergic inputs to the bulb indicate that they may have important roles in the control of odor-guided behaviors that are apparent during the earliest stages of postnatal life.

Development of the olfactory bulb: physiology

The newborn rat pup has mitral cells with dendrites synapsing onto receptor axons and axons forming connections with neurons in primary olfactory cortex. Electrophysiological studies have provided evidence that mitral cells are functional at birth, although their response properties differ somewhat from those of mitral cells in the mature rat. This discussion will focus on three aspects of odorant evoked activity: quality coding, or the specificity with which cells respond to different odorants; intensity coding, or the effect of odorant concentration on evoked responses; and inhalation-related timing, or the consistency with which units respond during successive stimulations or sniff-cycles.

Experimental studies have not provided a satisfactory description of the neural code for odor quality for either receptor or second order olfactory neurons in any vertebrate species[47]. Single unit studies have demonstrated that neurons in the mitral cell body layer of the adult rat respond to approximately 20% of substances used as stimuli[44,54], a degree of selectivity roughly comparable (given differences in experimental technique) to that observed for receptor and second-order olfactory neurons in other vertebrate species[47]. Unfortunately, no typologies exist that can provide a more precise definition of response specificity.

Odorant evoked responses of neurons in the olfactory bulb of the mature rat can be classified on the basis of the temporal pattern of activity evoked during the stimulus event[44,45]. The most prevalent kind, the type I response, is characterized by an increase in activity within 1 s of onset and lasting throughout the presentation of a weak odorant (fig. 2). At higher stimulus concentrations, the type I response consists of two bursts of action potentials separated by a relatively quiet period. Type II responses are characterized by diminished activity during the presentation of a low concentration of odorant and by a brief period of decreased activity followed by a sudden burst of action potentials for stronger stimuli. The latency of this post-inhibitory excitation decreases in a monotonic fashion as stimulus concentration is increased. Type III responses are characterized by diminished activity throughout the stimulus event at all odorant concentrations. The different concentration-dependent patterns of activity described for the rat are consistent with results reported for bulb neurons in other vertebrate species[24,38,51,73] and are different from those olfactory receptor neurons, described above.

Macrides and Chorover[42] recorded bulb units in mature rodents during stimulation with long trains of controlled inhalations similar to the odor sampling behavior of these animals during bouts of exploratory sniffing. They demonstrated consistent, odorant-specific patterns of activity that were temporally synchronized to the nasal inhalation cycle and they argued that inhalation-synchronized timing of activity is a more consistent and sensitive measure of odorant-evoked activity than is the average rate of neural activity during the presentation of a stimulus. In a series of subsequent studies, Macrides and his coworkers have presented evidence that exploratory sniffing is time locked to the limbic theta rhythm and they have hypothesized that the processing of olfactory information within the bulb and primary olfactory cortex is synchronized by the theta-rhythm through the efferent connections of its presumed generator, the medial septum/diagonal band complex[38,39,43]. Although limbic theta may have an important role in synchronizing the activity of olfactory areas of the brain, consistent, inhalation-related patterns of activity can also be observed when animals are stimulated with artificial sniffs that do not correspond to this rhythm. Figure 3 shows averaged peristimulus time histograms for two type I units driven by ethyl acetate during two successive stimulations[45]. For each histogram, the interstimulus interval is different. Nevertheless, the responses evoked have a consistent double-peaked pattern even when the number of evoked action potentials varies between the successive stimulus events.

As in the adult, the activity of bulb neurons in the rat pup seems to be closely related to nasal airflow. When pups are allowed to sniff on their own, mitral cells respond to

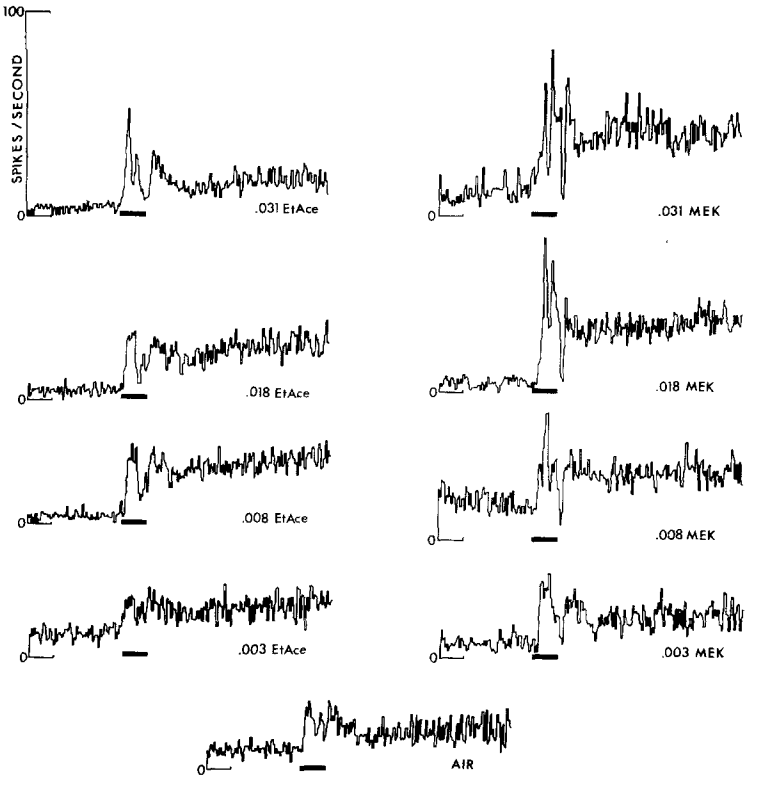

Figure 2. Averaged peristimulus time histograms of a Type I response recorded from a bulb neuron in an adult rat evoked by various concentrations of ethyl acetate (EtAce) or methyl ethyl ketone (MEK). Concentrations are in fractional vapor saturation. Stimulus events were two seconds in duration and are indicated by the heavy lines under each histogram. Reprinted from Mair[44].

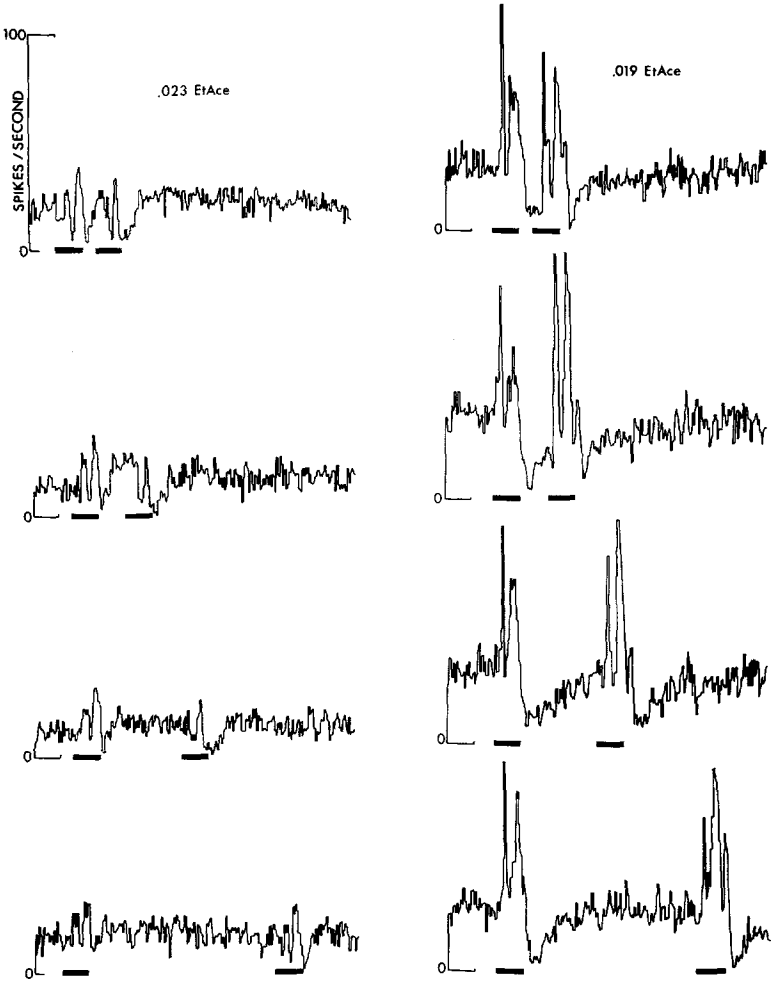

Figure 3. Averaged peristimulus time histograms of Type I responses recorded from two neurons during consecutive presentations of ethyl acetate at various inter-stimulus invervals. Concentration was .023 X vapor saturation for unit on left and two seconds in duration and are indicated by the heavy lines at the bottom of each histogram. Reprinted from Mair[45].

about 19% of pure chemical stimuli presented at the external nares[48]. Most responses are excitatory and these are driven in strict synchrony with the respiratory cycle[48]. Figure 4 shows a typical record from a pup on the third postnatal day (P-3) for a unit driven by ethyl acetate. Greater numbers of action potentials are evoked by increasing concentrations of ethyl acetate and the bursts occur at a consistent phase of the respiratory cycle (shown in the lower trace of each recording). With this same preparation, Mair and Gesteland[48] described two other apparent effects of respiratory behavior on the activity of bulb neurons. First, spontaneous neural activity was observed to fluctuate with shifts in the average rate of respiration. Second, several cells stopped firing action potentials during periods of altered respiratory activity presumably caused by strong odorous stimulation (fig. 5). Thus in the rat pup, the timing of respiratory activity has an apparent influence on the level of background activity as well as the timing of odorant evoked responses.

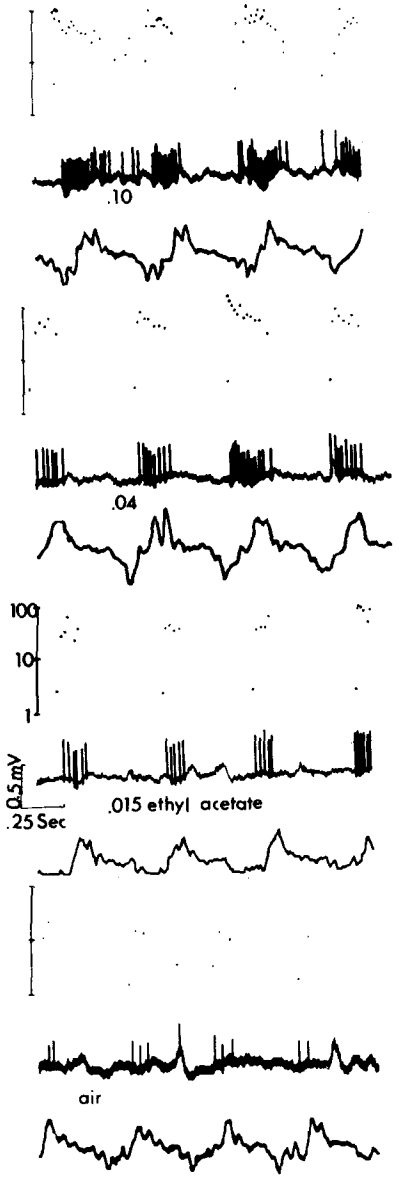

Figure 4. Activitiy recorded from a rat on postnatal day 3. Each record is photographed directly from an oscilloscope with the lower trace showing respiratory activity, the middle trace action potential activity of a bulb neuron, and the upper trace a continuous record of log instantaneous activity of that neuron (spikes/second). Animal was stimulated with various concentrations of ethyl acetate delivered to the external nares. Concentrations are in fraction vapor saturation. Reprinted from Mair and Gesteland[48].

The relationship between stimulus concentration and evoked activity was difficult to determine in preparations in which the pup sniffed odorants on its own. In some cases, the number of action potentials evoked increased with stimulus magnitude (fig. 4) and in others neural activity was suppressed and respiratory activity altered during the presentation of high concentrations of odorous substances (fig. 5). To study intensity coding in the newborn pup, Mair and Gesteland[48] used hypothermic surgery to expose the olfactory epithelium and they were thus able to control the duration of the stimulus event and to record summated receptor activity (EOG) while studying the response properties of units in the olfactory bulb. Units recorded in this preparation responded with approximately 28% selectivity to the pure chemicals used as stimulus substances. These neurons did not exhibit the response types characteristic of the adult[44,45]. Rather, their response patterns were similar to those exhibited by receptor neurons[17]. Figure 6 shows a typical example. Stimulation with .001 X vapor saturation of ethyl acetate resulted in small EOG deflections and a small increase in neural activity. At higher stimulus concentrations (.002, .008, and .032 X vapor saturation) the amplitude of the EOG increased and the number of evoked action potentials increased (.002 and .008) and then decreased (.032). For the strongest stimuli, bulb neurons tended to respond with a brief burst of action potentials followed by relatively quiet period. This pattern is similar to that described for receptor cells (fig. 1) and differs from responses described for neurons in the developed olfactory bulb[44,45]. On the basis of these data, Mair and Gesteland[48] have argued that prior to the maturation of bulb interneurons, mitral cells can respond selectively to odorous stimulation and transmit, with little modification, the temporal patterns of activity exhibited by receptor neurons.

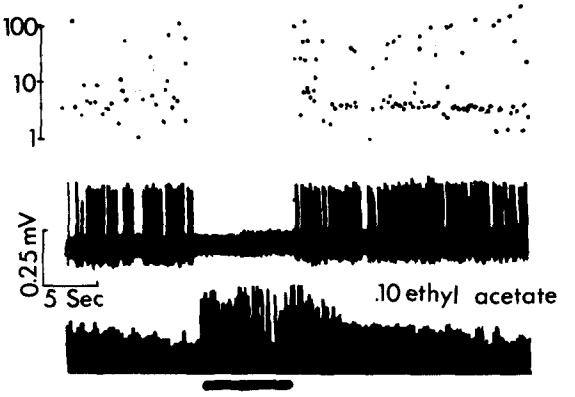

Figure 5. Respiratory activity (lower trace), action potential firing (middle trace) and log instantaneous activity (upper trace) of a bulb neuron in a rat on postnatal day 3 during stimulation with an 8 second presentation of .10 X vapor saturation of ethyl acetate. Reprinted from Mair and Gesteland[48].

Summary and speculations

In the rat, presumed mitral cells, in all regions studied of the olfactory bulb, respond selectively to odorous stimuli on the first day of postnatal life[48]. At this age, mitral cells receive inputs from receptor cells, which appear morphologically and physiologically mature, and they form synapses with neurons in, at least, limited regions of primary olfactory cortex. Thus, after just three weeks of gestation, the afferent pathway from receptor epithelium to primary olfactory cortex appears to be capable of mediating odor discriminations, even though it lacks practically all of the interneuronal pathways and many of the efferent connections characteristic more mature animals. Behavioral studies have shown that neonatal rat pups perform behaviors guided by chemosensory cues and can learn preferences and aversions for novel chemical stimuli. Although the relative importance of the olfactory and vomeronasal systems in these early behaviors is not certain, it is clear that second order olfactory neurons are capable of mediating these discriminations.

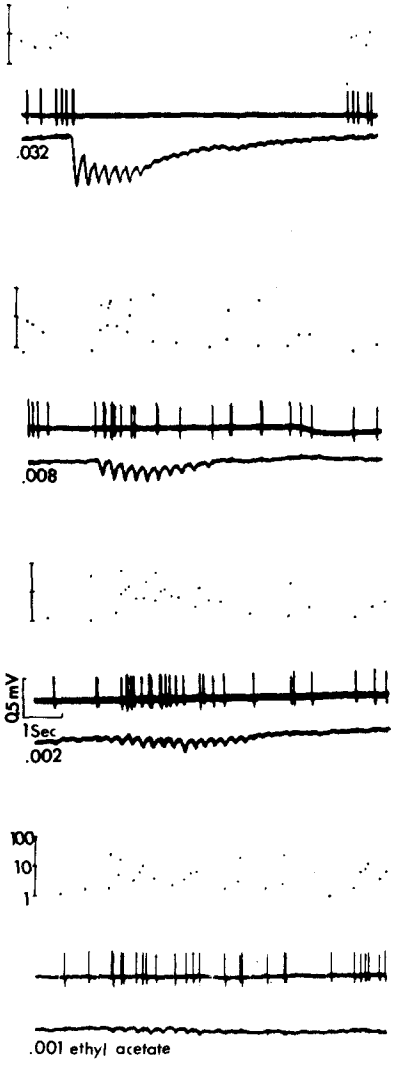

Figure 6. Electro-olfactogram activity (lower trace), unitary bulb activity (middle trace), and log instantaneous activity (upper trace) recorded from a rat on postnatal day 6. Nasal cavities were opened and stimuli delivered directly to the exposed epithelium. Concentrations are in fractions of vapor saturation. Reprinted from Mair and Gesteland[48].

If, for the sake of argument, we ignore the vomeronasal system and presume that the olfactory system mediates the early odor-guided behaviors of the rat, we can make several assertions about the functional properties of the olfactory system. First, interneuronal circuitry, including the extensive reciprocal pathways between the bulb and areas of primary olfactory cortex, is not necessary for simple odor discrimination learning. Although the adult rat undoubtedly has more olfactory capabilities than the newborn, the remarkable abilities of the pup places important limitations on the types of functions which might be ascribed to these connections. The role of the granule cell is particularly intriguing. It appears that the first granule to mitral cell synapses are being formed around the time of birth and, according to Kaplan and Hinds[37], these cells continue to be formed in significant numbers and incorporated into the circuitry of the bulb throughout, at least, early adult life. Given the apparent discriminating capacity of mitral cells in the newborn, the argument that granule cells sharpen the response characteristics of mitral cells by a process like lateral inhibition is not convincing. If the developmental data are taken seriously, then one must consider the possibility that granule cells have functions that appear at a later age, such as the mediation of centrifugal inputs; or that evolve throughout life, such as adjustments to different chemosensory environments or the storage of odor memories. Second, centrifugal inputs to the bulb mature at different ages and their development may correspond to the emergence of different odor-guided behaviors during early postnatal life. In newborn animals, the bulb receives inputs from many neurons in the locus coeruleus and relatively fewer cells in the nucleus of the diagonal band and the raphe[74]. There is a body of literature that implicates norepinephrine (NE) in attentional aspects of learning and memory for both humans and experimental animals[50]. The early development of noradrenergic inputs to the bulb is intriguing in view of evidence that treatments affecting brain NE (as well as DA) activity influence the acquisition of odor-guided behaviors in neonatal rats[7,52,59]. Taken together, these data raise the possibility that the release of NE in the olfactory bulb is critically involved in the early learning processes of the rat.

Divac[13] has presented evidence that the neurons projecting to the bulb from the nucleus of the diagonal band are a part of the chain of the magnocellular nuclei of the basal forebrain, which contain acetylcholine and (collectively) send projections to areas of cortex, brainstem, and olfactory bulb. Although the functions of these cholinergic nuclei are not known, Rolls et al.[67] have presented electrophysiological evidence that neurons in these areas of the brain mediate sensory aspects of feeding behavior. If this is the case, then the appearance of cholinergic markers in the bulb during the second postnatal week may correspond to the appearance of sensitivity to satiety that is first seen among pups of about that age[8,23]. The adult rat has numerous centrifugal fibers that arise in areas of primary cortex and terminate in the olfactory bulb that are of unknown functional significance. Given the time of their postnatal origin, the developing rat pup may provide a useful preparation for studying their behavioral functions.

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The olfactory bulb and central pathways

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Key words. Odor biology; olfactory bulb; piriform cortex; mitral cells; tufted cells; mediodorsal thalamus; olfactory tubercle.

This review of central olfactory system structure and function will concentrate on pathways involving the vertebrate main olfactory bulb. Other species and issues, including the vomeronasal system, are discussed in other reviews of this series.

The olfactory periphery

There is a rapidly expanding literature on the olfactory receptors and receptor processes that is outside the scope of this review. However, it is important to note the spatial localization of odor responses and the spatial organization of projections from the epithelium to the olfactory bulb.

Odor sensitivity is differentially localized on the receptor sheet. This localization is determined by the position of the receptor cell relative to the air flow[78] and by intrinsic properties of the receptor cell[42, 62, 76, 83]. The olfactory epithelium projects topographically to the olfactory bulb[10, 15, 20, 50, 63] maintaining the spatial localization of the peripheral odor response in the first stage of central projection. A crude spatial segregation of odor responsiveness has also been demonstrated with 2-deoxyglucose in the olfactory bulb of rats[9, 40, 128] and tree shrews[123].

The olfactory bulb

The olfactory bulb is a laminated structure with a generally ellipsoid form in the mammal. The figure illustrates the layers as described in the rat and hamster. Certain differences exist in other species. This description of the layers follows that by Shepherd[119, 120] and many details not mentioned here can be found in his reviews. The four major cell types of the bulb will be introduced first and their details developed in the description of the layers.