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Development of the Vestibular System

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Abstract
This review mainly focuses on the development of the vestibular system in humans and other mammals, but reference is made to anurans and other species where applicable. In the first section, the steps involved in the development of undifferentiated cells into mature vestibular receptors are analysed. Available data indicate that in humans, maturation of the vestibular receptor and its afferent innervations involves a similar sequence of events as in other mammalian species. In the second section, morphological and physiological aspects of the maturation of the central vestibular system are presented. Undifferentiated neuron precursors have been identified in specific segregrated domains of the hindbrain neural tube, and these can develop into secondary vestibular neurons with unique properties. Several neuronal populations in the vestibulospinal and vestibulo-ocular pathways have been found to correlate with rhombomeric domains at early embryonic stages. In rodents, the vestibular system continues to develop postnatally in terms of morphology and function until it achieves its final form. The postnatal changes in the properties of vestibular nuclear neurons are chronologically matched with structural changes and serve to prime the development of vestibular-induced reflexes.

The time course of the maturation of hair cells and their afferent innervation patterns in the vestibular system has been fully documented in histological and ultrastructural studies in a number of animal species, such as rats [1, 2] and mice [3–9], as well as in humans [10]. Comparison of different maturational events in humans and other animals is of particular interest. Through these correlations, it is possible to extrapolate from experimental results in animals to predict what may occur in the human vestibular system.

Development of the Peripheral Vestibular System

Ontogeny of Vestibular Hair Cells

In humans, the sensory epithelium remains undifferentiated until week 7 of gestation [9, 10]. At 7 weeks, nascent hair bundles can be seen in the central zone of the immature sensory epithelium, indicating that a few hair cells have begun their differentiation. The emerging hair bundle is formed by a group of cilia of the same length and has no precise polarity, i.e. the kinocilium cannot be distinguished from the stereocilia [11]. This arrangement is characteristic of what has been described as the initial stage of formation of the hair tuft in the mouse [12]. Most of the sensory epithelium in mouse vestibular organs is composed of a pseudo-stratification of undifferentiated cells at E14 [12, 13]. From embryonic day 14 (E14) to postnatal day 2 (P2), terminal mitoses of hair cells and

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supporting cells occur, with a peak at E16 [14]. By E16, immature hair cells with short stereocilia are evident [6]. Morphological differentiation into type I and type II hair cells starts at E19 in the mouse [3], while this developmental stage appears in the 11th to 13th week of gestation in humans [11]. Type I and type II hair cells have different cell shapes [4, 15], hair bundle geometry [16, 17] and voltage-gated conductance [18–21]. In the mouse utricle, type I hair cells, but not type II hair cells, are characterized by a large K^+ conductance ($g_{K,L}$) that is activated at unusually negative voltages [8, 21]. This conductance is absent at birth, but begins to be expressed at P4 [4].

Using autoradiography to trace the chronology of the normal development of rat vestibular receptors, Sans and Chat [22] demonstrated that maturation of the hair cells is more precocious (1) at the centre than at the periphery of the utricular maculae, and (2) at the apex than at the base of the cristae. In the embryonic stage, the maturation gradient of hair cells as described by terminal mitoses [22], ciliogenesis [5] and synaptogenesis [13] is also consistent with the developmental appearance of neuron-specific enolase and calbindin-D28K (protein markers that respectively indicate differentiation and synaptic activity of neurons) in the vestibular epithelium of the mouse [23] and human [24]. In the mouse [25], these changes parallel the morphological sequence of maturation from apex to base in the cristae and centre to periphery in the maculae [24, 26]. In summary, the maturation of the vestibular receptor, which is mature before birth in humans [11], involves a similar sequence as in other mammalian species.

Innervation of Vestibular Hair Cells

In the mouse, afferent and efferent nerve endings at the vestibular receptors are first identified at E17 and E18, respectively [13, 27]. Numerous unmyelinated afferent fibres contact hair cells at their base, forming flat and vesiculated terminals. These early hair cell-afferent fibre contacts develop into synapses characterized by the presence of synaptic bodies within the hair cells [9, 11]. An increase in the number of synaptic bodies at the beginning of synaptogenesis has also been observed in the human fetus between the 9th and 10th week [11]. In the mouse, partial calyces endings are seen as early as E18 [27]. Full calyces endings are first present in significant numbers some days after birth in the mouse [7, 28] and at the 20th week of gestation in humans. In the mouse, myelination of the peripheral afferent fibres starts on the day of birth, well after the first observation of synapses in the vestibular epithelium on E16 [13]. This process appears to be the final maturational event in the peripheral vestibular system and is not yet complete by P7. The exact time of maturation, however, remains to be ascertained.

In the late embryonic stages in the mouse, more efferent endings are found to be making contact either directly on the hair cells or on nerve calyces. The amount of efferent endings, however, has not yet reached its adult abundance at this stage [11, 29]. Immunohistochemical and confocal microscopic results have demonstrated that the efferent innervation pattern in rats continues to develop between P9 and P12 [29, 30]. In this postnatal period, however, animals exposed to a microgravity environment showed no plastic changes in the organization of the vestibular efferent network in the utricle [31]. In adult animals, it has been proposed that the vestibular efferent innervations provide modulatory control of signal transduction between the hair cells and the afferents [30, 32–34]. Efferent activation in the toadfish was found to result in an elevation of afferent activity such that the rectified response to acceleration became bidirectionally responsive without a change in response sensitivity [32]. A decrease in the number of clipped otolith neurons with age has also been attributed to the maturation of the efferent system [35], which only fully develops in the third postnatal week [36]. Nonetheless, the contribution of the efferent system to the postnatal maturation of vestibular function awaits further study.

Morphophysiological Correlations

Morphophysiological experiments carried out with intracellular injections of horseradish peroxidase in adult monkeys indicated that the response characteristics of the functionally identified afferent axons closely correlate with the location of their terminal field in the vestibular epithelium [37, 38]. For example, calyx units, which contact only type I vestibular hair cells in the central zone of the epithelium, were found to be discharging irregularly [38]. However, dimorphic units, which innervate both type I and II hair cells, exhibited different discharge regularities depending on their location on the macula. More irregularly discharging afferents were found to innervate the striola region than in the peripheral extrastriola region of the utricular macula [38]. In response to sinusoidal head rotations, calyx units and irregularly discharging dimorphic units showed larger phase leads and, hence, more phasic response dynamics than regularly discharging dimorphic units. Such differences are related to regional variations in the transduction mechanism of hair cells [38]. The results suggest that the response characteristics of functionally identified afferent axons are largely

determined by the status of vestibular hair cells and their innervation pattern.

The correlation between the morphology of afferent terminals and their spontaneous activity has also been studied in the mouse during the first postnatal week [39]. Development of the innervation pattern was characterized by labelling the afferents with intracellular injections of horseradish peroxidase performed between E17 and P10 [3]. This developmental stage corresponds to middle and late synaptogenesis between vestibular hair cells and primary afferent nerve terminals [10, 13]. In the mouse, the initial stages of synaptogenesis take place during the embryonic period [6, 10, 13] and seem to coincide with the end of terminal mitosis in hair cells [14]. On day 20 of gestation, the first endings differentiated into boutons or calyces [3]. The afferent innervation on the hair cells developed rapidly during the first 5 postnatal days. The proportions of the three types of units (i.e. calyx, bouton and dimorphic units) on P10 were comparable to those described in the adult chinchilla [40]. These results correlate with the physiological maturation of both canal-related and otolith-related vestibular afferents, as detailed in the following section.

Functional Development of Primary Vestibular Neurons

Recording of primary vestibular neuronal activity in the course of postnatal development has been performed mainly in vivo in the rat [41–44] and the cat [45], and in vitro in the mouse [39, 46]. In early postnatal life, some canal afferent neurons in the rat exhibited slow, irregular and near-zero spontaneous activity at rest, punctuated by random, unpredictable bursts of spikes [42, 43]. Increases in the mean resting discharge rate as well as in the proportion of canal regular units have been observed in the kitten [45] and in the rat [42, 43]. In the rat, regular activities appeared on P4, and the mean resting rate continued to increase steadily, reaching adult levels in the third postnatal week. In adult rats, about 32% of primary canal neurons fired regularly, and the mean resting discharge rate of these regular neurons was significantly higher than that of irregular neurons [42]. During postnatal development, there was also an increase in the response sensitivity of the canal afferent system and a progressive change in the response dynamics. With the use of long-duration constant angular acceleration, Curthoys [43] showed that the canal system was not very sensitive at birth, but its sensitivity increased rapidly after birth and became close to that of adults by P4. In the first postnatal week, primary canal neurons also showed a rapid increase in response gain during sinusoidal rotations and a slower decrease in phase lag [43]. Since the dynamic characteristics are related to the transduction mechanism of hair cells [37, 38], the phase-lag response pattern observed in neonatal rats [43] is correlated with the development of the hair cells and their afferent innervation patterns [46].

More recently, the functional properties of otolith afferents have also been examined in young and adult rats [47]. In early postnatal life (before P12), otolith afferents displayed a lower spontaneous firing rate and a more irregular discharge pattern than in older rats. Some vestibular afferents also showed a rhythmic bursting firing pattern with almost equal interspike intervals within bursts and interburst intervals [47]. Such a burst firing pattern, however, was not observed after P14. In contrast to reports of canal afferents [42, 43], no regular afferents were found in the first postnatal week. Regular activities were only observed in otolith afferents on P9, 5 days after the first appearance of regular canal afferents [42]. Reasons for the late appearance of regular activities in the otolith system, however, are still unclear. Further experiments are required to delineate whether there exists a differential maturation profile between the peripheral canal system and the otolith system.

Development of the Central Vestibular System

Afferent Projection to the Vestibular Nuclei

In mammals, vestibular afferents that innervate the vestibular hair cells form part of the eighth cranial nerve, which enters the brain stem at the level of the inferior cerebellar peduncle and terminates primarily within the vestibular nuclei. In the classical description of the vestibular system, vestibular neurons in the hindbrain are grouped into nuclei on the basis of cytoarchitectonic features such as cell size, shape and distribution [48, 49]. The vestibular nuclear complex can be subdivided into four main nuclei, namely the superior, lateral, medial and descending or spinal [48]. Vestibular nerves enter the vestibular nuclear complex at the level of the lateral vestibular nucleus [50], where they typically bifurcate into a descending tract that branches within the medial and descending vestibular nuclei and an ascending tract which terminates in the superior vestibular nucleus as well as sending projections to the cerebellum (primarily the uvula and nodulus) [see ref. 51 for a review, 52, 53].

During development in all vertebrates, the embryonic hindbrain neuroepithelium is organized at the gross morphological level as a series of segments known as rhom-

bomeres [54–56]. In larval frogs, vestibular afferent fibres enter the brain stem at rhombomere 4, split up into ascending and descending fibre bundles and terminate in the dorsal hindbrain between rhombomere 1 and rhombomere 8 in a region corresponding to the vestibular nuclear complex of adult frogs [57, 58]. Of the four main vestibular nuclei, the superior vestibular nucleus appears to derive from larval rhombomere 1/2, the lateral vestibular nucleus from rhombomere 3/4 and the major portions of medial and descending vestibular nuclei from rhombomeres 5–8 [59].

Anatomical studies have demonstrated the spatial and temporal sequence of proliferation gradients in the vestibular nuclear complex [60] and the temporal sequence of dendritic and somatic growth and synaptic formation within the lateral vestibular nucleus of the rat [61, 62] and humans [63]. Altman and Bayer [60] reported that the differentiation of neurons within the vestibular nuclei in rats occurs between E11 and E15 and follows latero-medial and rostro-caudal internuclear gradients. Peak production time is E12 in the lateral vestibular nucleus, E13 in the superior nucleus, E13–E14 in the descending (or spinal) nucleus and E14 in the medial nucleus [60]. Thus, the development of these nuclei seems to be linked to the relative importance of their roles in the early embryo. The lateral and descending vestibular nuclei, involved in postural stabilization from birth, mature before the superior and medial nuclei, which are involved in gaze stabilization, which appears 2 weeks later [60]. In humans, although neurons in the lateral vestibular nucleus have been distinguished from glia after 16 weeks of gestation [63], the pattern of differentiation of neurons within the vestibular nuclei is still unclear.

Functional Development of Central Vestibular Neurons

The postnatal development of spontaneously active medial vestibular neurons, which can be distinguished by after-hyperpolarizations into type A and type B, has been characterized in mouse brain slices [64]. Without inputs from the vestibular nerve, these medial vestibular neurons displayed intrinsic pacemaker-like membrane conductances that generated resting activity [65–68]. At P5, both the type A and the type B neurons were found to exhibit immature forms of action potential. During postnatal development, the single after-hyperpolarization in type A neurons gradually became deeper, and the early fast after-hyperpolarization appeared in type B neurons at P15 [66]. In addition, the apamin-sensitive slow after-hyperpolarization which induces burst firing in immature type B cells appeared as early as P5, indicating that the Ca^{2+}-activated K^+ current is one of the first conductances to regulate the intrinsic rhythmicity and excitability of these neurons during early postnatal life.

In addition to the contribution of sustained K^+ currents to the distinct firing pattern of central vestibular neurons, another cellular feature that regulates the resting activity of vestibular nuclear neurons is the activity of N-methyl-*D*-asparate (NMDA) receptors [69, 70]. In particular, the discharge regularity of neurons in brain stem slices has been shown to be modulated by the activation of NMDA receptors [71], which operate more effectively in the early postnatal period than in adults [70, 72]. Furthermore, developing neurons differed with respect to the time course of expression of NMDA receptor subunits [73]. This suggests that NMDA receptors may trigger the processes underlying the change in neuronal excitability during postnatal development.

The postnatal properties of canal-related vestibular nuclear neurons have been characterized in rats [74, 75]. During postnatal development, the resting discharge rate of neurons increased steadily from a very low and irregular firing pattern in neonates to reach a high and more regular state by the end of the first postnatal month. In very young rats (P4), some cells displayed random bursts of spikes. The response sensitivity of these neurons to angular acceleration also matured progressively, reaching the adult level at the end of the first month [74, 75].

The properties of central otolith neurons in coding head movements near the horizontal plane have been studied in postnatal [35, 76–78] and adult rats [77, 79–81]. With the use of such natural stimuli as off-vertical axis rotation (OVAR) [77, 78, 82–85] and horizontal linear acceleration [79–81], the best vectors of central otolith neurons of adult animals were found to point in all directions on the horizontal plane. Such a uniform spatial distribution was also observed in the cerebellar fastigial nucleus [82] and medial medullary reticular formation [86] of adult cats. However, an imbalance of spatial response patterns between the bilateral vestibular nuclei was observed following the restriction of otolith inputs by hemilabyrinthectomy [87, 88]. This finding implies that in the normal state, where both labyrinths are intact, the crossed otolith signals serve to complement and supplement inputs arising from the ipsilateral otolith. During development, the contribution of the vestibular nuclei on both sides in coding head movements, however, is still unknown.

Recently, the development of vestibular nuclear neurons in coding head movements was studied in postnatal

rats [35, 76, 89]. In these studies, OVAR was used to selectively stimulate the otolith by introducing a rotating gravity vector around the head [90]. All central otolith neurons displayed position-dependent changes in the firing rate during 360-degree OVAR, indicating their capability to code spatial information during low-frequency head movement [35]. However, the capacity of central otolith neurons to code head movements in neonatal rats is lower than the adult level. These neurons undergo progressive changes both in their resting discharge and spatiotemporal properties during postnatal development [89]. At P7, the vast majority of central otolith neurons showed irregular discharge patterns. As the rats matured, the overall population showed more regular patterns [35, 78]. Spontaneous activities of the neurons in the stationary position were analysed in relation to their response gains during otolith activation, and a positive correlation was observed from P14 onwards [35]. In rats older than P14, the best response orientation of central otolith neurons was found to point in all directions close to the horizontal plane, indicating that all head orientations on this plane were encoded within the vestibular nucleus [77, 78, 82]. At P7, however, central otolith neurons particularly tuned for the pitch response were not well developed. The vector orientations were found to distribute predominantly along the interaural axis (i.e. roll direction), indicating that the newborn rat's ability to code head positions with respect to gravity is more restricted than the adult's [76]. The mechanism underlying the temporal disparity in coding the roll and pitch information within the vestibular nucleus of postnatal rats remains to be resolved. However, it should be noted that the postnatal development of the spatial coding properties of central otolith neurons seems to be correlated with motor behaviour development. During postnatal development, lateral movement could be recorded at P2 [91]. Vertical movement was absent until P9, when the rats succeeded in turning their head upward in response to passive downward tilting [92]. This reaction was shown to be mature in the middle of the second postnatal week [92, 93]. By P14, vertical movement of the whole body was observed and the animals were able to sit on their hind legs [36]. These features are chronologically matched with the emergence of pitch neurons within the lateral and descending vestibular nuclei during postnatal development [76].

It has been shown that otolith stimulation has a strong effect on systemic circulation and vagal activity [94]. Studies of the cardiovascular and respiratory response to vestibular stimulation in adult cats have demonstrated that tilts near the pitch plane are optimal for these reflexes [94, 95]. The absence of pitch information in central otolith neurons of young rats may imply the immaturity of the vestibulo-autonomic system.

In future studies, it would be of interest to correlate the morpho-electrophysiological features of central vestibular neurons with their projection patterns during the development of otolith function. This will enable us to unveil the maturation profile and functional connectivity among components of the central vestibular system.

Development of Vestibulospinal and Vestibulo-Ocular Projections

At early stages of embryonic development, vestibular nuclear neurons with specific axonal projection targets are localized to specific, segregated rhombomeric domains of the hindbrain neural tube in the chicken [96–98]. More recently, the two specific sets of vestibular neurons, namely the vestibulo-ocular and the vestibulospinal neurons, were identified in rhombomeres of embryonic chicks [99], frogs [59] and rats [100, 101]. These studies provide a ground-plan for elucidating the development of the connectivity patterns of the vestibular system [97].

At E11 in chicks, the vestibulo-ocular projection has a wider rostro-caudal distribution in the brain stem than the vestibulospinal projection [102]. The vestibular nuclear neurons are segregated according to their projection to either oculomotor or spinal cord targets, with minor overlap. Very few vestibular neurons project to both targets, as shown from injections of double fluorescent labels [102]. In chicks, the initial development of the dual projections in the secondary vestibular neurons may therefore occur later than E11 [102]. The development of such a dual projection pattern in the vestibular nuclei of postnatal mammalian species is still unexplored. The dual projections of secondary vestibular axons in the medial longitudinal fasciculus to extra-ocular motor nuclei and the spinal cord have been described, however, in adult squirrel monkeys [103].

Vestibulospinal Pathways

Vestibular signals are relayed to spinal motor centres via the lateral vestibulospinal tract (LVST) and medial vestibulospinal tract (MVST) [104]. The MVST originates primarily in the medial nucleus, joins the medial longitudinal fasciculus and projects bilaterally and monosynaptically to motoneurons in spinal lamina 7 throughout the cervical and upper thoracic levels. Through the MVST, the semicircular canal nerve has both excitatory and inhibitory disynaptic connections with the neck motoneurons [105–107]. Some of the utricular nerve-acti-

vated vestibulospinal neurons also project through the MVST, and their axons terminate mainly in the upper cervical segments [108]. Several experiments also showed that the saccular projection to neck extensor motoneurons was mainly via the MVST [109–111].

The LVST, originating primarily in the lateral vestibular nucleus and the rostral part of the spinal vestibular nucleus, descends in the ventral part of the ventral funiculus to lumbar levels and terminates in spinal laminae 7 and 8 of the ventral horn [112, 113]. About 73% of the utricular-activated vestibulospinal neurons project through the ipsilateral LVST and reach the cervico-thoracic junction and the lumbar spinal cord [108]. Moreover, 30% of saccular-activated vestibulospinal neurons send axons through the ipsilateral LVST to the upper cervical spinal cord [110], and disynaptically to the extensor neck motoneurons [111]. The semicircular canal nerve makes inhibitory trisynaptic connections with some neck motoneurons through the LVST [114, 115]. In addition, the caudal parts of the medial and spinal vestibular nuclei give rise to a third vestibulospinal projection, the caudal vestibulospinal tract [116]. The function of this pathway, which appears to project bilaterally to all levels of the spinal cord, is still unclear. However, it has been reported that about 7% of the saccular nerve-activated vestibulospinal neurons project through the caudal vestibulospinal tract and terminate in the upper cervical segments [110].

Studies performed on E11 chicks demonstrated the development of two major longitudinal pathways from the vestibular nuclei to the upper cervical spinal cord, namely the MVST and the LVST [97, 98, 117]. At the embryonic stage, the contralaterally projecting vestibulospinal neurons in the MVST are localized largely to rhombomere 5 but with a substantial component in the lateral portion of rhombomere 4 [99]. The ipsilateral MVST group, however, is localized to rhombomere 6, with a minor spillover [99]. In both chick and rodent embryos, the cell bodies of the ipsilateral LVST are clustered in a region corresponding to rhombomere 4, with a minor spillover into rhombomeres 3 or 5 [101, 118].

During development, the vestibulospinal neurons send their axons to the LVST and MVST, which have been segregated into various segments of the spinal cord both anatomically and physiologically [119–122]. In addition, the vestibulospinal neurons can be distinguished by their genetic characteristics [123]. In brief, the genesis of the vestibulospinal neurons occurs firstly in the lateral vestibular nucleus at E12 in the rat, then in the descending vestibular nucleus at E12–E13 and finally in the medial vestibular nucleus at E13–E14. Cells of the MVST remain proliferative at E12–E14, and neurons show great diversity in their projection targets and fibre courses [123]. In contrast, cells of the LVST are proliferative only at E12, and neurons are more uniform in their projections [124, 125]. The time of ingrowth of vestibulospinal axons into the spinal cord has also been studied in various species. In *Xenopus laevis,* there is a rostro-caudal gradient such that more caudally situated cells project their axons sooner to the spinal cord [126]. In zebra fish [127] and rats [36], however, laterally placed large neurons project their axons earlier than the small, medial neurons.

After birth, the vestibulospinal pathways continue to develop. In rats, 50% of the total LVST axons originating in the lateral vestibular nucleus are present on P2 and 88% of them reach the lumbar enlargement by P15 [36]. This finding is in agreement with the developmental projection of the vestibulospinal neurons to the cervical and lumbosacral cord segments in neonatal rats [128–130]. In addition, Clarac et al. [36] indicated that the development of the vestibular afferents and descending pathways in the first 2 postnatal weeks is essential to the maturation of the postural and locomotor functions.

Development of the Vestibulospinal Reflex

The head-turning response (cephalic response) to angular accelerations in the horizontal plane has been studied in postnatal rats [131]. This response, generated by the stimulation of the horizontal semicircular canals, increases gradually from the first to the seventh day of postnatal life without any visual influence [131].

In rats, the head-turning response appears earlier than the air-righting reflex, which is provoked by linear acceleration acting on the macular receptors [132, 133]. During postnatal development, it has been shown that the air-righting reflex does not appear until about P6–P7 [36, 134, 135] and is not complete until about P14–P16 [132]. The air-righting response is not a simple reflex, as it involves not only maturation of the peripheral and central vestibular systems but also the capability of the motor system to organize the behavioural response [132, 136]. Air-righting can only be viewed as a demonstration of purely vestibular righting in the absence of tactile influence [137] in species that do not use vision to trigger righting, e.g. the rat [138]. The mouse, rat and rabbit show a similar time course of maturation of the righting reflex. The righting reflex in the rabbit, for example, appears at P3, develops rapidly between P7 and P11 and reaches the adult level by P15 [139].

Vestibulo-Ocular Pathways

In humans and other vertebrates, many vestibular nuclear neurons project to the extraocular motor nuclei [51–53], largely via the medial longitudinal fasciculus [48]. These vestibulo-ocular pathways [140, 141] provide a close link between the hair cells on the semicircular canal and the extra-ocular muscles for the generation of compensatory eye movements [142]. When compared with the wealth of information about the projections from the semicircular canal to extra-ocular motoneurons, only a few studies have described the pathways of otolith-ocular reflexes [143–147]. With regard to utriculo-ocular reflex arcs, Imagawa et al. [144] and Uchino et al. [146] demonstrated disynaptic connections between utricular primary afferents and ipsilateral abducens nucleus neurons. In addition, polysynaptic connections from the utricular afferents to contralateral trochlear motoneurons has been reported [145]. By means of intracellular recording, Uchino et al. [147] demonstrated the presence of polysynaptic long latency connections between the utricular nerve and motoneurons innervating superior and inferior oblique muscles. In the sacculo-ocular pathway, only 3% of the saccular-activated vestibular neurons studied had direct ascending branches to the oculomotor nucleus [110]. Uchino et al. [111] suggested that saccular afferents seem to have polysynaptic linkages to extra-ocular motoneurons.

In larval frogs, retrograde labelling of the medial longitudinal fasciculus just caudal to the midbrain oculomotor complex revealed several subgroups of vestibular neurons that correspond to distinct adult vestibular nuclei [59]. The superior vestibular nucleus is the only source of bilateral oculomotor and trochlear projections in the rostral hindbrain. Vestibular neurons within the lateral and descending nuclei send fibres either ipsilaterally or contralaterally to the oculomotor complex [59]. In larval frogs, midbrain-projecting cells within the superior vestibular nucleus are clustered in a rhombomeric region corresponding to ipsi- and contralateral rhombomere 1/2 [59]. In chick embryos, rhombomeres 1 and 2 both contribute bilaterally to the pool of midbrain-projecting cells within the superior vestibular nucleus [99, 148]. However, the ipsilateral ascending projections from rhombomere 3 in chicks [99], goldfish and zebra fish [149] represent an homologous rostral portion of the lateral vestibular nucleus. The ipsilateral oculomotor-projecting cell clusters in rhombomere 5 are comparable to a population of rostral descending vestibular nuclear neurons in adult chicks [150] or to neurons in the tangential nucleus in pigeons [151]. The contralaterally projecting neurons in rhombomeres 6–8 project to the trochlear and rostral oculomotor nuclei [152].

Development of the Vestibulo-Ocular Reflex

In the newborn kitten, stimulation of the ipsilateral vestibular nerve has been shown to evoke monosynaptic excitatory postsynaptic potentials and disynaptic inhibitory postsynaptic potentials in abducens motoneurons, while stimulation of the contralateral vestibular nerve produced disynaptic excitatory postsynaptic potentials [153], indicating that the basic vestibulo-ocular neuronal pathway is functional at birth. Moreover, high-frequency electrical stimulation of the vestibular nerve can elicit conjugate eye movements even in newborn rats [154], showing that the more central components of the vestibulo-ocular pathway are mature enough to be activated. However, it is not known whether natural stimulation of the vestibular receptor (i.e. rotation of the head) is able to elicit the vestibulo-ocular reflex (VOR) in newborn rats [154]. In rats [154], kittens [155] and rabbits [156], vision is not essential for the development of the VOR. The VOR can be elicited in rats well before their eyes open (15 days after birth) [154], and visual deprivation also has no effect on the maturation of the VOR. However, it seems that vision is necessary to achieve perfect compensatory eye movements over a wide frequency range of optokinetic stimulation [156].

These results show that the VOR can be activated in newborn animals immediately after birth. The decrease in threshold in eliciting the VOR during postnatal growth [154] is closely paralleled by changes in the dynamic characteristics of primary [42, 43] and central canal neurons [74]. In addition, it should be noted that only a few studies have reported the development of the otolith-ocular reflex in neonatal rats. It is still unknown whether the progressive change in properties of otolith-related vestibular nuclear neurons during the first 3 postnatal weeks contributes to the development of the otolith-ocular reflex [35]. Tegetmeyer [157] demonstrated that in conscious rabbits (P3), however, the eye muscles are capable of responding to static tilt stimulation for the stabilization of gaze.

In humans, the vestibular system is anatomically mature by the 5th month of gestation [11]. However, the VOR in children is quantitatively different from that in adults [158–160]. There is a marked modification of the VOR throughout childhood [for a review, see ref. 161]. In response to angular acceleration, for instance, newborn infants show distinct nystagmus, characterized by alternating slow and fast components, and reach the adult level after the first few months of life [161, 162]. An interest-

ing phenomenon is that in children, the canal-ocular reflex and otolith-ocular reflex, elicited by vertical axis rotation and OVAR, respectively, develop independently of each other [160]. The canal-ocular reflex parameters (i.e. the time constant and the highest initial slow phase velocity) remain unchanged after birth, while the otolith-ocular reflex parameters (i.e. the amplitude of the modulation and the bias of the slow phase velocity) change with age, especially at the stage when children are learning to walk [160]. This finding implies that in children, the ability to walk is paralleled by a change in the otolith but not the canal response.

Conclusion

In comparison to other sensory systems, developmental studies of the vestibular system are relatively scarce. Exhaustive studies of the peripheral vestibular system are required to determine the functional significance of electrophysiological features in developing vestibular neurons and to correlate these with the structural and biochemical changes within the cell itself and within the terminal field of the hair cells. Further experiments are needed in the central vestibular system to clarify the pattern of vestibular circuitry by identifying afferent and efferent connections and their time of synaptogenesis. Also, experiments should be designed to correlate the morphology of growing neurons with their membrane and synaptic properties as they develop into mature entities. These are crucial for understanding how vestibular information is established in the brain during development.

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