Vestibular Nuclei and Their Cerebellar Connections

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Abstract

The vestibular nuclei and the vestibulocerebellum comprise the anatomical crossroads where primary vestibular information is collected, stored, and modified by other sensory inputs (visual, proprioceptive, autonomic) and central cortical commands. Secondary vestibular neurons are clustered into five nuclei in which different subsets of vestibular primary afferents terminate. This distributed organization may be based on the targeted outputs of the clustered secondary neurons rather than on selective afferent targeting. Vestibular primary and secondary afferent mossy fibers activate a large mediolateral extent of granule cells in multiple folia of vermal lobules IX–X. However, the vermal and hemispheric lobules IX–X are organized in three dimensions by vestibular and visual climbing fiber inputs that are arrayed in narrow sagittal strips. In vermal lobules IX–X, these climbing fiber strips encode linear acceleration imposed by changes in head movement with respect to gravity using the utricular otoliths and angular acceleration of the head about the anatomical axes of the two vertical semicircular canals. Hemispheric lobule X encodes self-motion using climbing fiber structured optokinetic feedback imposed by the three axes of the semicircular canals. Vestibular and visual adaptation of this circuitry is needed to maintain balance during postural perturbations. Secondary neurons in the vestibular nuclei and cerebellar neurons may contribute to storage and modification of postural reflexes. Compensation of postural reflexes following unilateral damage to the vestibular nerve provokes changes in cellular expression of protein kinase C-δ without causing a change in transcription of PKC-δ mRNA.

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8.1 Introduction

The cerebellum and vestibular nuclei are two major components of a larger neural system that controls how vestibular information is received, how it is stored, and how it is modified. This review describes connections between the cerebellum and vestibular nuclei that are multiple and complex.

8.2 Vestibular Nuclei

Five vestibular nuclei are located just below the dorsal surface of the medullary brainstem (Fig. 8.1A$_1$). They include descending, lateral, medial, and superior nuclei (DVN, LVN, MVN, and SVN) as well as the parasolitary nucleus (Psol). All five vestibular nuclei receive a mixture of ipsilateral vestibular primary afferents. Each vestibular nucleus is differentiated by a combination of cytological features, axonal boundaries, cell sizes, and immunohistological characteristics. The DVN, LVN, MVN, and SVN contain a variety of cell types. The LVN contains the largest neurons in the brain, Dieter's neurons, whose soma are ~50 μm in diameter. The LVN also contains many smaller cell types (Brodal and Pompeiano 1957; Brodal 1974; Barmack et al. 1998a). This variability in cell size within a nucleus is regional, suggesting that these nuclei may have multiple circuits and functions. At the other extreme, neurons in the Psol are uniformly small, 5–7 μm in diameter, and are immunolabeled by an antiserum to glutamic decarboxylase, the synthetic enzyme for the neurotransmitter gamma amino butyric acid (GABA) (Barmack et al. 1998b). The distributed organization of the vestibular nuclei may be based on common targeted outputs rather than on selected afferent targeting of homogeneous circuitry.

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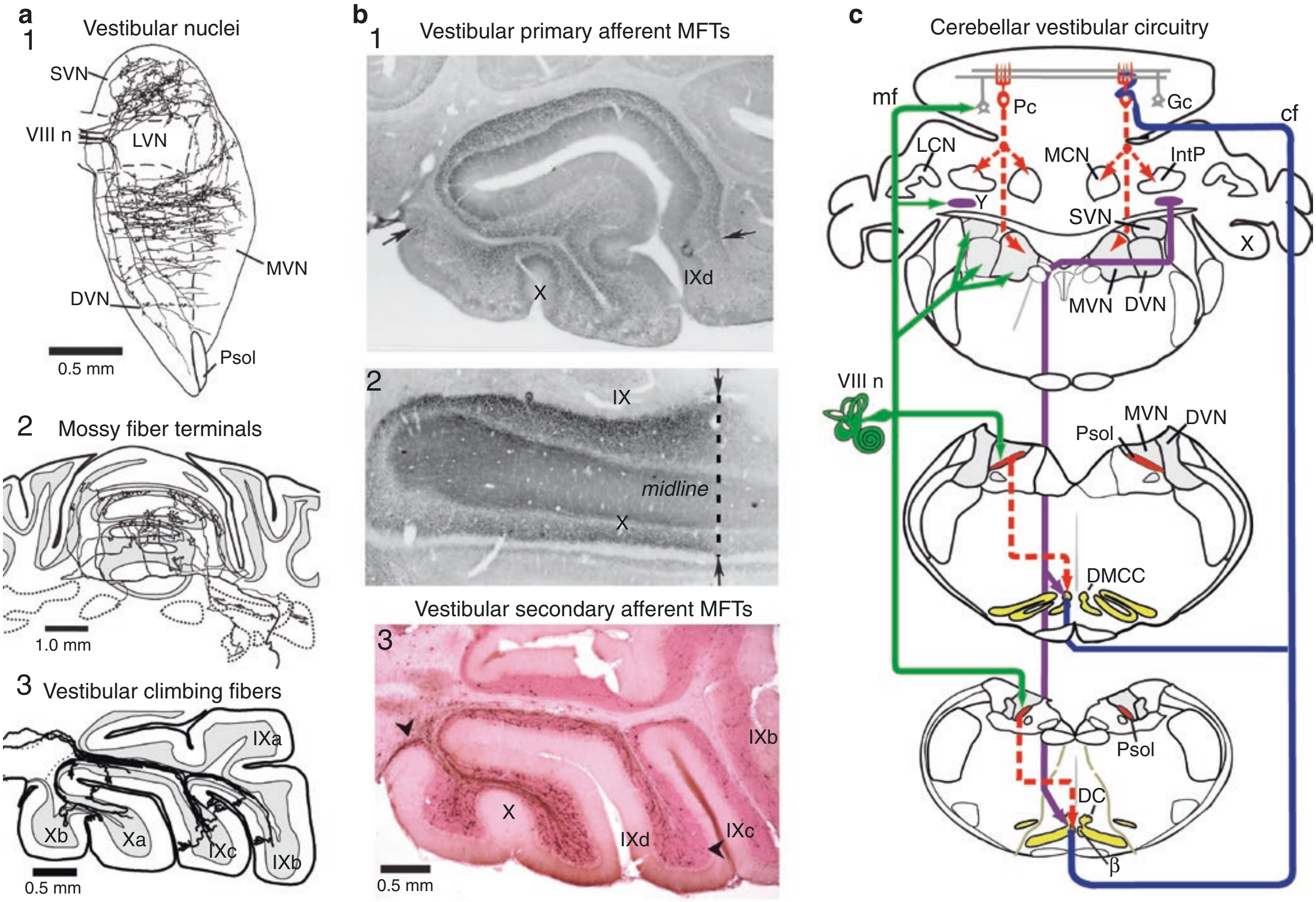


Fig. 8.1 Projections of vestibular primary and secondary mossy and climbing fiber afferents to the vestibular nuclei and lobules IX–X and how these projections are embedded in cerebellar circuitry. (**A$_1$**) Viewed dorsally, five horizontal semicircular canal afferents, intra-axonally labeled with HRP project to all vestibular nuclei except the LVN. Modified from (Sato and Sasaki 1993). (**A$_2$**) Mossy fiber terminals from a BDA-labeled lateral reticular nucleus neuron project bilaterally as they reach the anterior cerebellar vermis. (**A$_3$**) Sagittal view of several BDA-labeled climbing fibers that project in narrow sagittal bands to the contralateral lobules IX–X. Modified from (Wu et al. 1999). (**B$_1$**) Vestibular primary afferents are labeled with the C fragment of tetanus toxin (TTC) injected into the left labyrinth of rabbit. TTC is transported orthogradely and trans-synaptically and labels MFTs and granule cells in lobules IX–X. Arrows bracket the regions of profuse labeling. Note absence of labeling in other folia. (**B$_2$**) A horizontal section through lobules IX–X shows that the projection of TTC-labeled vestibular primary afferents is unilateral. Modified from (Barmack et al. 1993b). (**B$_3$**) Vestibular secondary afferents, labeled with an injection of WGA–HRP into the caudal medial and descending vestibular nuclei, reveals labeling of mossy fiber terminals in lobules IX–X. (**c**) Schematic illustrates the vestibular mossy (green) and climbing fiber (blue) projections to the brainstem and posterior cerebellar cortex. Vestibular primary afferent mossy fibers (**mf**) (green) project to the ipsilateral parasolitary, medial, descending, superior vestibular nuclei (**Psol**, **MVN**, **DVN** and **SVN**). GABAergic Psol neurons (dashed red lines) project to the ipsilateral β-nucleus (**β**) and dorsomedial cell column (**DMCC**) in the inferior olive (yellow). Y-group neurons (**Y**) (purple) project to contralateral **DC**, **β** and **DMCC** (purple lines). Neurons in **β** and **DMCC** project as climbing fibers (blue) (**cf**) to contralateral lobules VIII–X. Modified from (Barmack and Yakhnitsa 2000). *cf* climbing fiber, *DC* dorsal cap, *LVN* lateral vestibular nuclei, *Gc* granule cell, *LCN*, *IntP* and *MCN* lateral, interpositus and medial cerebellar nuclei, *Pc* Purkinje cell, *mf* mossy fiber, *Nsol* nucleus solitarius

8.3 Cerebellum

Lobules IX (uvula) and X (nodulus), including the hemispheric X (flocculus), are the principal, but not exclusive cerebellar focus for interactions with vestibular nuclei. The circuitry embedded within these lobules is engaged by three distinct vestibular inputs. (1) Granule cells within vermal lobules IX and X receive a vestibular primary afferent collateral mossy fiber projection from every ipsilateral vestibular primary afferent. (2) A vestibular mossy fiber projection to granule cells in both vermal and hemispheric lobules IX–X is bilateral and originates from vestibular secondary mossy fiber afferents from the vestibular nuclei. (3) A third pathway to vermal lobule X is conveyed by vestibular climbing fibers (Fig. 8.1A$_3$). Vestibular climbing fibers originate from two subnuclei of the contralateral inferior olive, β-nucleus, and dorsomedial cell column. The dendritic tree of each Purkinje cell receives ~500 synaptic contacts from a single climbing fiber. However, a single climbing fiber may synaptically contact the dendritic trees of as many as 15 Purkinje cells.

The vestibular climbing fiber projections to vermal lobules IX–X (uvula, nodulus) are arrayed in two narrow sagittal strips that encode vestibular space in two rotational axes encoded by the anterior and posterior semicircular canal ampullae and utricular otoliths (Fig. 8.1A$_3$, c). The width of these climbing fiber strips is ~0.4 mm in the mouse and ~1.0 mm in the rabbit. A third axis, rotation encoded by the horizontal semicircular canal ampullae is absent (Fushiki and Barmack 1997; Barmack and Yakhnitsa 2003).

A similar array of sagittal climbing fiber strips, encoding a three-dimensional optokinetic space, originates from the dorsal cap (DC) of the inferior olive and projects onto hemispheric lobule X (flocculus). The coordinates of these spaces correspond physically to the planar orientation of the three semicircular canals (Simpson et al. 1981; Van der Steen et al. 1994; Billig and Balaban 2004; Foster et al. 2007; Yakusheva et al. 2010).

8.4 Vestibular End Organs

The peripheral vestibular apparatus consists of three semicircular canals and two otoliths. The semicircular canals are oriented orthogonally and sense angular acceleration about horizontal, vertical, and oblique axes. Otoliths (saccule and utricle) sense linear acceleration imposed by movement of the head with respect to the gravitational vector during roll-tilt of the head about the longitudinal axis (utricle) and during pitch about the intra-aural axis (saccule).

8.5 Vestibular Primary Afferent Cerebellar Projections

Each vestibular endorgan contributes primary vestibular afferents to the vestibular nerve that branches into two fiber bundles of unequal thickness as they enter the brain stem. The thicker fiber bundle enters the medulla between the ventral aspect of the inferior cerebellar peduncle and the dorsal aspect of the spinal tract of the trigeminal nucleus. It turns caudally and passes into the vestibular complex to terminate on secondary vestibular neurons. The thinner fiber bundles branch as the primary afferent passes through the inferior cerebellar peduncle and then though superior and lateral vestibular nuclei. The thinner branch ascends to the cerebellum where it terminates as mossy fiber terminals on granule cells in ipsilateral vermal lobules IXd–X (Cajal 1911) (Fig. 8.1A$_1$, B$_{1, 2}$). The unilateral projection of vestibular primary afferent mossy fibers is shown best using the trans-synaptic orthograde tracer, Tetanus toxin C fragment (TTC), injected into a labyrinth. TTC is orthogradely transported to the cerebellum where it labels only ipsilateral mossy fiber terminals and granule cells (Fig. 8.1B$_{1, 2}$) (Barmack et al. 1993b).

8.6 Vestibular Primary Afferents' Projections to Vestibular Nuclei

Primary afferents of the main branch terminate in each of the five vestibular nuclei (Brodal and Pompeiano 1957; Brodal 1972, 1974; Barmack et al. 1998a; Barmack and Yakhnitsa 2000) (Fig. 8.1A$_1$). Within the cerebellum, vestibular primary afferents branch again and distribute mossy fiber terminals (MFTs) both sagittally and medio-laterally within vermal lobules IXd–X. The mossy fiber branching pattern is illustrated best by the spatial patterning of MFTs that originate from the lateral reticular nucleus (LRN) labeled with biotin dextran amine (BDA) (Wu et al. 1999) (Fig. 8.1A$_2$). A single mossy fiber branch develops ~40 MFTs that contact dendrites of ~15 granule cells. In total, a single mossy fiber makes synaptic contact with ~600 granule cells (Palkovits et al. 1972). Primary and secondary vestibular afferents account for ~90% of the total mossy fiber projection to vermal lobules IXd–X (Korte and Mugnaini 1979; Kevetter and Perachio 1986; Gerrits et al. 1989; Sato et al. 1989; Barmack et al. 1993b; Akaogi et al. 1994; Purcell and Perachio 2001; Newlands et al. 2002, 2003; Maklad and Fritzsch 2003).

The projection of primary afferent MFTs to vermal lobules IX–X is not restricted to a single folium. Vestibular primary afferent MFTs from, say, the left posterior semicircular canal (LPC), project primarily not only to left vermal lobule X, but also, more sparsely to left vermal lobule IXd. The left saccule projects to the left vermal lobule IX, but more sparsely to the left vermal lobule X (Maklad and Fritzsch 2003). This widely distributed pattern of projections of vestibular primary afferent MFTs creates regions within lobules IX–X where MFTs from a particular endorgan may be concentrated, but not exclusively represented. For example, neurons that respond to stimulation of the ipsilateral anterior semicircular canal are found in the SVN more laterally than are neurons in the SVN that respond to stimulation of the ipsilateral posterior semicircular canal (Abend 1977). Horizontal semicircular canal primary afferents project to the DVN, MVN, and SVN, but not the LVN and Psol. The activity of Psol neurons is driven by stimulation of ipsilateral anterior and posterior semicircular canals, as well as the ipsilateral utricle. However, Psol activity is not driven by stimulation of the horizontal semicircular canals. Secondary neurons within the LVN receive a primary vestibular projection from the ipsilateral saccule, but not from the utricle (Sato and Sasaki 1993).

8.7 Visual Projections to Vestibular Nuclei

Vestibular primary afferents comprise only one of the sensory inputs to the vestibular complex. Most secondary vestibular neurons are also driven by visual (optokinetic) stimulation (Henn et al. 1974). Although visual signals to the vestibular nuclei originate from a variety of brainstem and cortical sources, the best understood pathways by which optokinetic signals reach the vestibular nuclei originate from the accessory optic system (AOS) (Simpson et al. 1988). Direction selective retinal ganglion cells project to the AOS. AOS neurons, in turn, project to vestibular nuclei, the cerebellum, and the inferior olive. The AOS also receives a descending projection from the visual cortex. In primates, this projection originates from the pre-striate cortex (areas OAa and PGa) (Ilg and Hoffmann 1996). Selective stimulation or inactivation of this region modifies the directional selectivity of neurons in the AOS.

8.8 Neck-Proprioceptive Afferents to Vestibular Nuclei

Signals from proprioceptors embedded in the intertransverse muscles at the base of the cervical vertebrae activate secondary vestibular neurons (McCouch et al. 1951; Hikosaka and Maeda 1973). Injection of HRP into the caudal MVN and DVN retrogradely labels neurons in ipsilateral C_2–C_3 spinal ganglia and in the contralateral central cervical nucleus and bilaterally in C_1–C_6 dorsal horn cells (Bankoul and Neuhuber 1990; Sato et al. 1997). Neurons in the vestibular complex also receive secondary cervical afferents relayed through the external cuneate nucleus (Ecu) (Prihoda et al. 1991). Movement of the head with respect to the body stimulates neck proprioceptors and evokes reflexive eye movements as well as postural adjustments of the limbs (McCouch et al. 1951; Hikosaka and Maeda 1973; Barmack et al. 1981).

8.9 Autonomic Influences of the Vestibular Nuclei

The vestibular nuclei not only participate in reflexes mediated by skeletal muscles, but also are part of the circuitry through which autonomic reflexes (blood flow, respiration rate, and heart rate) are regulated (Rossiter et al. 1996; Kerman et al. 2000; Kaufmann et al. 2002). Specifically, this circuitry includes projections from the caudal vestibular nuclei (DVN, MVN and Psol) to the solitary nucleus (Nsol). The Nsol receives autonomic afferents, from the heart, esophagus and stomach, carried chiefly by branches of the IX and X cranial nerves.

8.10 Internal Connections Within the Vestibular Nuclei

The pattern of interconnections within the vestibular complex has been mapped with microinjections of HRP into the vestibular complex of the rabbit. Interconnections between the SVN–DVN and SVN–MVN are reciprocal (Epema et al. 1988). A group of larger neurons in the rostro-ventral MVN, SVN, and LVN receives inputs from smaller cell regions of MVN, SVN, and DVN, but do not reciprocate (Ito et al. 1985). The MVN has a non-reciprocal projection to the DVN.

8.11 Bilateral Connections Between Vestibular Nuclei

The vestibular nuclei, with the exceptions of the LVN and Psol, are interconnected through a commissural system. The commissural projections are multiple. First, a primary afferent that projects to one nucleus may also project to the same or different contralateral nucleus. Second, the commissural projections of secondary vestibular afferents are not restricted to homotypic nuclei. Rather, cells within a nucleus on one side of the brainstem, say the left MVN, project to the contralateral SVN and DVN as well as the contralateral MVN (Epema et al. 1988; Newlands et al. 1989; Wayman et al. 2008). Electrical stimulation of the utricular macula evokes excitation in ipsilateral secondary vestibular neurons and inhibition in more than 50% of the contralateral secondary vestibular neurons. Only 10% of secondary neurons responsive to ipsilateral stimulation of the saccule are inhibited by contralateral saccular stimulation. These data support the idea that the utricles are wired reciprocally, while the saccule are not.

8.12 Ascending Projections of Vestibular Nuclei

Targets of secondary vestibular afferents are diverse. Secondary afferents from the DVN and MVN project to both vermal and hemispheric lobules VIII–X, the anterior vermis, and paraflocculus (Thunnissen et al. 1989; Epema et al. 1990). Most of these ascending projections are cholinergic (Tago et al. 1989; Barmack et al. 1992a, b, c).

Neurons in rostral DVN, MVN, and SVN provide an ascending input to cranial motor nuclei III, IV, and VI, controlling the reciprocal contractions of extraocular muscles (Deecke et al. 1977; Büttner and Lang 1979; Graf et al. 1983; Büttner-Ennever 1992). Other brainstem nuclei that receive ascending projections from secondary vestibular neurons include nucleus Darkschewitsch, sensory trigeminal nucleus, interstitial nucleus of Cajal, and the sub-parafascicular complex (Barmack et al. 1979). The sub-parafascicular complex also projects reciprocally to the ipsilateral MVN.

Several ascending projections to the thalamus originate from the rostral part of the vestibular complex to the ventral-basal thalamus (VPL, VPM and VPI). Neurons in the ventral-basal complex are driven by stimulation of deep proprioceptors and joint receptors as well as vestibular inputs (Deecke et al. 1977; Lang et al. 1979; Shiroyama et al. 1999; Bacskai et al. 2002). These thalamic nuclei, in turn, project to Areas 3aV and parietotemporal association cortices (Fukushima 1997). These cortical areas receive optokinetic and somatosensory inputs as well. The importance of this projection is illustrated by the observation that humans with damage to parietal cortex, and without visual cues, do not recognize true vertical (Leigh 1994). Vestibular cortices project reciprocally to vestibular nuclei, suggesting that these cortical regions may supersede reflexes evoked by primary vestibular afferents (Akbarian et al. 1993, 1994; Nishiike et al. 2000).

8.13 Cholinergic and GABAergic Secondary Vestibular Projections

A subset of vestibular secondary neurons is cholinergic and projects bilaterally to both vermal and hemispheric lobules IX–X as well as the nucleus prepositus hypoglossi (NPH) (Epema et al. 1990; Barmack 2003). NPH neurons, in turn, project bilaterally to the caudal vestibular nuclei as well as the inferior olive (McCrea and Baker 1985). The projection from NPH to the dorsal cap is both cholinergic and GABAergic (Barmack et al. 1993a; De Zeeuw et al. 1993).

Neurons in the Y-group, a group of cells distributed between the inferior cerebellar peduncle and the lateral vestibular nucleus, also receive bilateral projections from the SVN. The ventral division of the Y-group projects to the ipsilateral flocculus, nodulus, and contralateral oculomotor complex. The dorsal division projects contralaterally to the dorsal cap and beta nucleus of the inferior olive. This projection is excitatory (Kumoi et al. 1987). Y-group and NPH neurons project directly to the cerebellum as mossy fibers. Y-group and NPH neurons also influence the activity of neurons in the inferior olive that make overlapping projections to the cerebellum as climbing fibers.

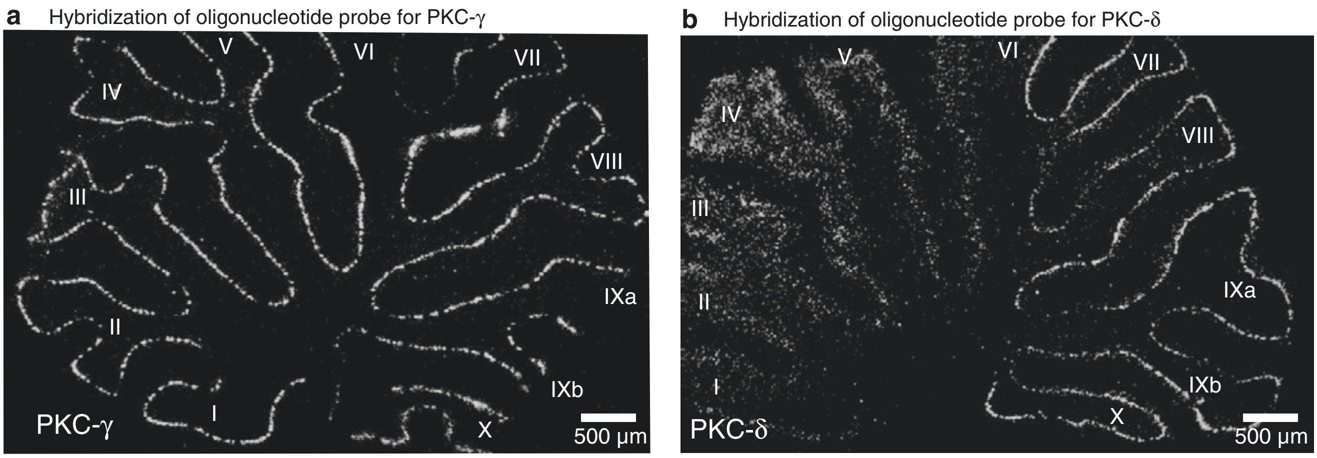
8.14 Descending Projections of Vestibular Nuclei

Descending lateral and medial vestibulospinal tracts originate from the LVN and MVN and DVN (Brodal 1981). The lateral vestibulospinal tract is organized within the LVN topographically. Fibers to the lumbosacral spinal cord originate from the dorsal-caudal LVN. Fibers to the cervical cord originate from the rostro-ventral LVN. Axons in the lateral vestibulospinal tract terminate in the ipsilateral lumbosacral region where they make monosynaptic and polysynaptic connections with motoneurons (Rose et al. 1992). Axons in the medial vestibulospinal tract terminate bilaterally in the medial part of the cervical ventral horn. The bilateral representation of vestibulospinal axons is most dense in the cervical enlargements from which motoneurons supplying the suboccipital muscles originate. These motoneurons participate in vestibulocollic reflexes.

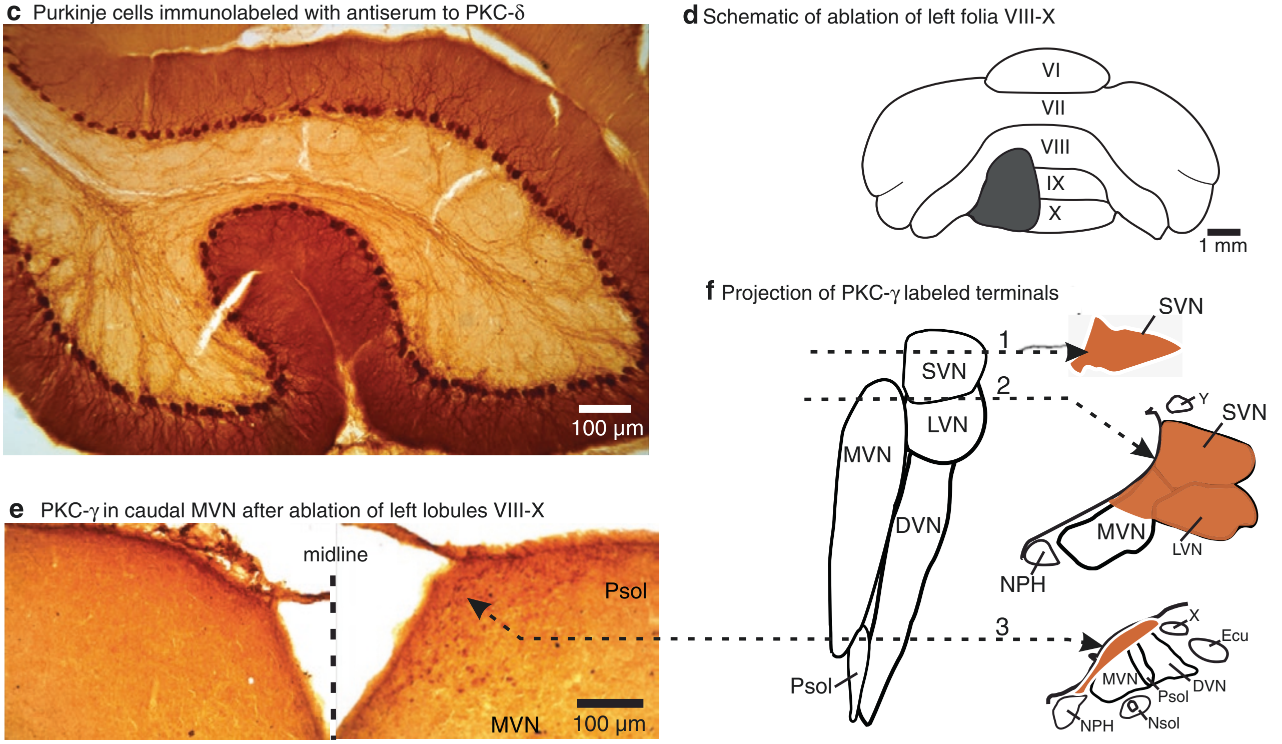
Psol neurons differ from the other vestibular nuclear neurons in that they make no secondary mossy fiber projections to the cerebellum. The output of Psol is GABAergic. It descends to the ipsilateral inferior olive where it modulates the activity of cells in the β-nucleus and dorsomedial cell column (DMCC) (Fig. 8.1c) (Barmack et al. 1993c, 1998a). These olivary neurons terminate as climbing fibers in the contralateral vermal lobule X. As they descend to the inferior olive, Psol axons distribute collaterals to nuclei in the reticular formation, particularly in the nucleus reticularis gigantocellularis (Fagerson and Barmack 1995).

8.15 Cerebellar Projections to Vestibular Nuclei

Cerebellar projections to the vestibular nuclei include, but are not restricted to lobule X (Walberg and Dietrichs 1988). While Purkinje cells project onto the same vestibular nuclei from which secondary vestibular mossy fiber projections originate, the reciprocal overlap is incomplete. This projection can be examined by labeling Purkinje cell axon terminals with a marker that is uniquely expressed by them and then mapping the regions of the vestibular complex where the marker is expressed. Protein Kinase C is a family of isoforms implicated in subcellular signal transduction. Several PKC isoforms (PKC-α, β, γ, δ, and ε) are expressed within major cerebellar cell types. Some are expressed in cerebellar projection target neurons, cerebellar nuclear neurons, and secondary vestibular neurons. Of all these isoforms, only two, PKC-γ and PKC-δ, are highly expressed in Purkinje cells and are not expressed in secondary vestibular neurons or cerebellar nuclear neurons (Barmack et al. 2000). PKC-γ is expressed in all Purkinje cells, whereas the expression of PKC-δ is restricted to lobules VI–X (Fig. 8.2a–c). Within the cerebellar nuclei, PKC-δ-immunolabeled Purkinje cell axon terminals are found within the medial aspect of the caudal half of the ipsilateral interpositus nucleus. Both PKC-δ and PKC-γ-immunolabeled axon terminals are found within the caudal MVN and DVN, Psol, and NPH. The projection patterns of PKC-immunolabeled Purkinje cells are confirmed by ablation experiments in which unilateral ablations of lobules VII–X deplete PKC-immunolabeled terminals in the vestibular complex ipsilateral to the ablation, but leave the terminals intact in the contralateral vestibular complex (Fig. 8.2d, e). LVN and SVN neurons also receive a uniformly dense projection of PKC-δ- and PKC-γ-immunolabeled axon terminals. This projection originates mostly from the "b zone" of the vermis (Andersson and Oscarsson 1978a, b). The "b-zone" receives climbing fiber projections conveying cutaneous information from the forelimbs and hind limbs (Bernard 1987; Shojaku et al. 1987; Walberg and Dietrichs 1988; Tabuchi et al. 1989).


a Hybridization of oligonucleotide probe for PKC-γ

b Hybridization of oligonucleotide probe for PKC-δ


c Purkinje cells immunolabeled with antiserum to PKC-δ

d Schematic of ablation of left folia VIII-X

e PKC-γ in caudal MVN after ablation of left lobules VIII-X

f Projection of PKC-γ labeled terminals

Fig. 8.2 Identification of Purkinje cell axon terminal projections to vestibular nuclei. (**a**, **b**) Sagittal sections through rat cerebellum are hybridized with an oligonucleotide probe for of PKC-γ (**a**) and PKC-δ mRNA (**b**). The PKC-γ probe hybridized with all Purkinje cells in lobules IX–X. The PKC-δ probe hybridized strongly with Purkinje cells in lobules VI–X. (**c**) A PKC-δ antiserum immunolabels Purkinje cells in lobules IX-X. (**d**, **e**) A unilateral ablation of left lobules VII–X, illustrated in (**d**) reduces PKC-γ immunolabeled Purkinje cell terminals projecting to the caudal left MVN (**e**). The Purkinje cell terminals in the right MVN, although sparse, remain intact. (**f**) Horizontal sections through the brainstem illustrate the anterior–posterior extent of the vestibular complex. Three transverse sections through the brainstem illustrate the presence of PKC-γ immunolabeled terminals in each division of the vestibular complex. The antero-posterior location of each section is indicated by the dashed lines (1–3). The density of immunolabeled Purkinje cell terminals is illustrated by brown overlays. *DVN, LVN, MVN SVN* descending, lateral, medial and superior vestibular nuclei, *Ecu* external cuneate nucleus, *NPH* nucleus prepositus hypoglossi, *Nsol* solitary tract nucleus, *Psol* parasolitary nucleus, *SpV* spinal trigeminal nucleus, *PO* posterior thalamic nuclear group, *VL* ventrolateral nucleus, *VM* ventromedial division of **LVN**, *VPL* ventral posterior lateral nucleus, *Y* Y-group. [Modified from (Deecke et al. 1977; Büttner and Lang 1979; Graf et al. 1983; Büttner-Ennever 1992; Barmack et al. 2000)]

Purkinje cell projections to MVN, NPH, SVN, DVN, and Psol are less complete, suggesting that many secondary vestibular neurons, particularly in the posterior half of the vestibular complex, operate independently of direct cerebellar feedback (Fig. 8.2f). The dorsal-caudal MVN and DVN receive dense projections from Purkinje cells in lobules IX–X. However, the descending cerebellar projection to the ventral divisions of the MVN, DVN, and Psol is sparse (Fig. 8.2f). Cells in this region of the MVN, DVN, and LVN give rise to the medial vestibulo-spinal tract.

8.16 Cerebellar and Vestibular Compensation

One of the classic attempts to understand interactions between the cerebellum and vestibular nuclei focuses on the change in postural stability following a unilateral labyrinthectomy (UL). The recovery following such damage is termed "compensation." Others have speculated that the vestibulo-cerebellum could ameliorate the consequences of the unilateral loss of vestibular primary afferents by reducing the discharge of ipsilateral Purkinje cell "simple spikes" (SSs) and thereby decrease the GABAergic inhibition of ipsilateral secondary vestibular neurons (McCabe and Ryu 1969). However, following a UL in the mouse, the discharge of Purkinje cell SSs decreases in contralateral (not ipsilateral) lobules IX–X (Barmack and Yakhnitsa 2013). This contralateral reduction of SSs can be attributed to a loss of spontaneous primary vestibular afferent activation of Psol neurons (Fig. 8.1c). This reduces inhibitory (GABAergic) signaling to inferior olivary neurons in the ipsilateral β-nucleus and DMMC, increasing the climbing fiber-evoked discharge of "complex spikes" (CSs) in contralateral Purkinje cells. The increased discharge of CSs in contralateral Purkinje cells decreases SSs, probably through climbing fiber-evoked stellate cell inhibition, thereby increasing the Purkinje cell-evoked GABAergic inhibition (Montarolo et al. 1982; Barmack and Yakhnitsa 2003, 2008, 2013). So, the immediate consequence of a UL is a reduction of activity of secondary vestibular neurons in the contralateral vestibular complex. The UL also causes a loss of vestibularly-evoked modulation of the discharge of CSs and SSs in Purkinje cells in contralateral lobules IX–X normally evoked by roll-tilt. This modulation is only slightly impaired in Purkinje cells ipsilateral to the UL. Chronically, the modulation of both CSs and SSs partially recovers.

8.17 Subcellular Evidence of Cerebellar Plasticity

When PKC expression is reduced in L7-PKC-mutant transgenic mice, long-term depression (LTD) is reduced in cerebellar Purkinje cells (Ito and Karachot 1992). Adaptation of the vestibuloocular reflex to altered conditions of optokinetic stimulation is also impaired (De Zeeuw et al. 1998).

Following a UL in rats, the immunolabeling of PKC-δ, of Purkinje cell axon terminals in the caudal ipsilateral vestibular complex decreases (Qian and Barmack 1996). After a UL, Western blots prepared from the ipsilateral uvula-nodulus show that cytosolic PKC-δ increases and membrane-associated PKC-δ decreases (Barmack et al. 2001). Hybridization histochemistry and semi-quantitative reverse transcription polymerase chain reaction (RT-PCR) demonstrate no change in transcription of PKC-δ and PKC-γ mRNA in the lobules IX–X after a UL. These data indicate that PKC-δ and PKC-γ are constitutively expressed, but that their distribution within Purkinje cells depends upon cellular activity.

Since PKC-δ is independent of calcium concentration, it could provide a regulatory signal for synaptic release that is independent of the calcium influx associated with excitation–secretion at synaptic terminals (Azzi et al. 1992; Sossin and Schwartz 1993). Alternatively, PKC has been linked to the regulation of the GABA transporter through a plasma membrane protein, Syntaxin 1A (Beckman et al. 1968). By modulating the GABA transporter, the interaction of PKC and Syntaxin 1A could influence the net release of GABA. Following a UL, compensation could occur if decreased Purkinje cell activity contributed to a decreased release of GABA, homeostatically compensating for the loss in primary afferent excitation of secondary vestibular neurons. Reduced expression of 14-3-3-θ and PKC-γ in Purkinje cells reduces the serine phosphorylation of $GABA_A\gamma_2$, critical for its insertion into the post-synaptic membrane (Qian et al. 2012).

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