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Intrinsic and synaptic plasticity in the vestibular system

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The vestibular system provides an attractive model for understanding how changes in cellular and synaptic activity influence learning and memory in a quantifiable behavior, the vestibulo-ocular reflex. The vestibulo-ocular reflex produces eye movements that compensate for head motion; simple yet powerful forms of motor learning calibrate the circuit throughout life. Learning in the vestibulo-ocular reflex depends initially on the activity of Purkinje cells in the cerebellar flocculus, but consolidated memories appear to be stored downstream of Purkinje cells, probably in the vestibular nuclei. Recent studies have demonstrated that the neurons of the vestibular nucleus possess the capacity for both synaptic and intrinsic plasticity. Mechanistic analyses of a novel form of firing rate potentiation in neurons of the vestibular nucleus have revealed new rules of plasticity that could apply to spontaneously firing neurons in other parts of the brain.

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Introduction

A fundamental challenge in learning and memory research is to understand how changes in cellular activity or molecular expression correspond with specific changes in behavior. Relating neuronal activity to perception or actions exhibited by awake behaving animals is a difficult task, partly because the complexity of most neural circuits precludes making direct links between cellular activity and behavioral consequences. These obstacles are largely reduced in the vestibular system, which provides an excellent model for cellular and molecular investigation of simple forms of learning.

The vestibular system is crucial for sensing self-motion and for stabilizing the eyes and body in space. Head motion signals are transduced by hair cells in the vestibular periphery and transmitted through the vestibular nerve to neurons in brainstem vestibular nuclei

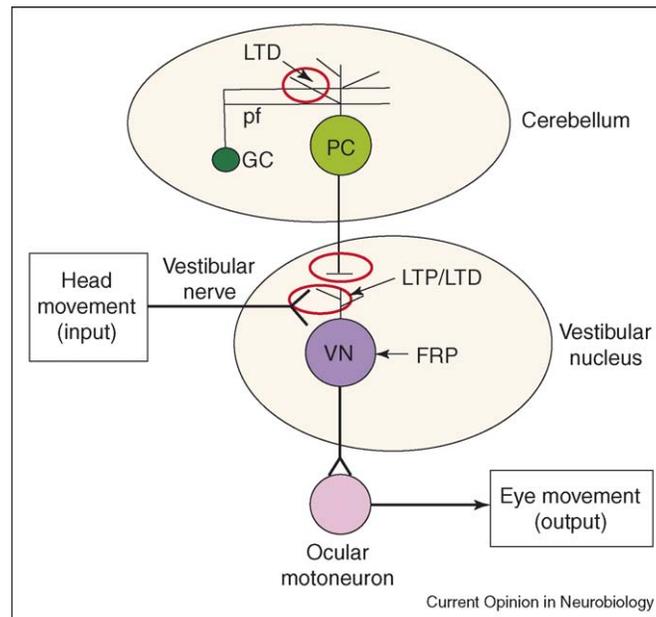
(Figure 1). Vestibular nucleus neurons contribute to a variety of circuits that are responsible for initiating compensatory movements of the eyes, head and body [1,2] in addition to providing information about head direction to forebrain circuits [3,4] and for signaling postural changes to the autonomic nervous system [5]. Several decades of electrophysiological recordings from the vestibular system have provided insights into the activity and roles of identified populations of neurons in both anesthetized and awake behaving subjects of a variety of species [6,7]. These investigations set the stage for making direct links between cellular and synaptic mechanisms and their consequences for behavior and learning.

Remarkable plasticity occurs in the vestibular system throughout life. Behavioral analyses of vestibular plasticity have focused primarily on the vestibulo-ocular reflex (VOR), which enables retinal images to remain stable during head motion by driving compensatory eye movements. Powerful forms of motor learning occur in the VOR whenever images move persistently on the retina during head movements. Learning in the VOR causes adaptive changes in the strength and/or timing of eye movements and can be quantified as changes in gain (ratio of eye speed to head speed) and phase (timing relationship between eye and head movement). In this review, we focus on cellular mechanisms that could contribute to learning in the VOR, with a particular emphasis on synaptic and intrinsic mechanisms of plasticity within the vestibular nuclei.

Cerebellar contributions to vestibular plasticity

The cerebellar cortex and deep cerebellar nuclei are crucial for motor learning. Purkinje cells in the floccular lobe of the cerebellum receive information about head and eye movement through parallel fiber synapses and information about image motion through climbing fibers from the inferior olive, and as such are well-positioned to sense the conjunction of signals that drive learning in the VOR. A long-standing hypothesis, that cerebellar learning depends on long-term depression (LTD) of synapses from parallel fibers onto Purkinje cells (Figure 1), has been tested directly in the context of VOR learning (reviewed in [8]). Targeted genetic disruption of LTD in Purkinje cells has little effect on baseline oculomotor behavior, but impairs short-term learning in the VOR that is induced by visual-vestibular mismatch training [9]. Interestingly, long-term learning in the VOR does not appear to rely on cerebellar LTD; both increases and decreases in VOR gain could be induced after multiple days of visual-vestibular mismatch training in

Figure 1



Sites of plasticity in vestibular circuitry. The basic neural connections underlying the vestibulo-ocular reflex (VOR) are indicated with thick black lines. Head movement information is carried by the vestibular nerve to neurons in the vestibular nucleus. These neurons then excite ocular motoneurons to drive compensatory eye movements. VOR plasticity involves a cerebellar circuit in which head movement information is transmitted to granule cells in the cerebellum through mossy fibers (not shown). The parallel fibers of granule cells then synapse onto Purkinje cells, the sole output neurons of the cerebellar cortex. LTD at the parallel fiber to Purkinje cell synapse (circled in red) could underlie early stages of vestibular learning. Additional sites of synaptic plasticity that probably play a role in consolidation and long-term storage of vestibular memories lie within the vestibular nuclei (circled in red). High frequency stimulation of the vestibular nerve can induce LTP and LTD at its synapses onto vestibular nucleus neurons. The probability of LTP and LTD at this synapse changes during development and shifts with experience. Synaptic plasticity might also occur at the projections from Purkinje cells onto vestibular nucleus neurons. Vestibular nucleus neurons also exhibit another form of plasticity, firing rate potentiation (FRP), expressed as increases in intrinsic excitability through reductions of a potassium current. Abbreviations: FRP, firing rate potentiation; GC, granule cell; LTD, long-term synaptic depression; LTP, long-term synaptic potentiation; PC, Purkinje cell; pf, parallel fibers; VN, vestibular nucleus neuron.

LTD-deficient mice, although gain increases were impaired when compared with those in wild type mice [10]. These findings add to the emerging view that many different mechanisms of plasticity support learning in the VOR [11–13], and that LTD is likely to contribute to the initial stages of learning [9,14]. A crucial role for LTD in the induction of learning is supported both by behavioral analyses of VOR learning in mice with genetic alterations in LTD signaling molecules [8[•],15^{••}] and by the finding that pharmacological blockade of cerebellar glutamate receptors precludes VOR learning [16].

Two interesting recent papers indicate that although the cerebellar cortex is required for the induction of oculomotor learning, the expression of long-lasting oculomotor memories resides in the vestibular nuclei [15^{••},17^{••}]. Decreases in VOR gain in cats evoked by a single, one hour session of visual–vestibular mismatch training were abolished after injection of the glutamate receptor blocker CNQX into the flocculus, indicating that synaptic excitation in the cerebellar cortex is required for the early expression of VOR memory [17^{••}]. Daily training sessions over multiple days evoked cumulative decreases in VOR

gain. Intriguingly, CNQX injections into the flocculus after 5 days of training had relatively little effect on the expression of VOR memory, such that only the recently acquired gain decreases were abolished by CNQX [17^{••},18]. These results suggest that although the initial expression of learning in the VOR requires synaptic excitation in the cerebellar flocculus, the maintained expression of consolidated VOR memories does not.

Remarkably similar results were obtained with a different oculomotor learning paradigm in mice [15^{••}]. Prolonged visual motion stimuli produce adaptive increases in the optokinetic reflex (OKR), which drives compensatory eye movements in response to full field visual motion. Exposure to one hour of patterned visual motion induced increases in OKR gain that were abolished by injections of lidocaine, a sodium channel blocker, into the cerebellar flocculus. After multiple, daily OKR training sessions, floccular injections of lidocaine affected only the most recently acquired increases in OKR gain, while sparing gain increases acquired during the previous training periods. These findings demonstrate that spiking activity in the flocculus is required for the expression of long-lasting

OKR memory. A surprising experimental result from this study supports previous claims from VOR learning studies in monkeys that oculomotor memories are stored in the vestibular nuclei [11,19]. After multiple days of OKR training, synaptic field potentials evoked in the vestibular nucleus by vestibular nerve stimulation were potentiated relative to control levels [15]. Although visual motion signals are not transmitted by the vestibular nerve [20], most vestibular nucleus neurons respond to optokinetic stimulation [21]. Potentiation of the vestibular evoked field potentials after OKR training is, therefore, likely to reflect learning-related changes in intrinsic excitability or synaptic transmission in visually responsive neurons of the vestibular nucleus.

Synaptic plasticity in the vestibular nuclei

Theoretical and experimental results from *in vivo* studies indicate that learning in the VOR is accompanied by synaptic plasticity in the vestibular nuclei [6,22,23]. The pronounced learning-related changes in response to head movements observed in neurons of the vestibular nucleus suggest that a predominant locus of plasticity is at synapses conveying head motion information, either directly from the vestibular nerve or indirectly through interposed neurons of the vestibular nucleus. Synapses from Purkinje cells onto their targets in the vestibular nuclei are also likely to be plastic. Neurons in the Y group, one of the vestibular nuclei responsible for vertical eye movements, receive synaptic inhibition from floccular Purkinje cells [24] (Figure 1). After the induction of learning in the VOR, Purkinje cells exhibited altered firing during eye movements, but their target neurons in the Y group did not [23]. The most likely explanation is a change in the efficacy of Purkinje cell synapses onto Y group neurons. Although activity-dependent changes in Purkinje cell synapses onto neurons of the vestibular nucleus have not yet been examined *in vitro*, a potential cellular analog has been found in plasticity of the analogous synapse onto neurons of the deep cerebellar nucleus [25–27].

In contrast to the extensive body of work on cellular studies of cerebellar cortex and deep cerebellar nuclei, relatively few groups have investigated cellular mechanisms of plasticity in the vestibular nuclei. The results to date indicate that a wealth of plasticity mechanisms exist within the vestibular nuclei, and a resurgence of interest in linking cellular mechanisms with their consequences for learning offers promise that the field will not lie fallow for long. The most thoroughly examined form of synaptic plasticity in vestibular nuclei involves long-term potentiation and depression (LTP and LTD) of the field potential responses to vestibular nerve stimulation [28] (Figure 1). In mature rats, high frequency stimulation of vestibular nerve axons in brainstem slices evokes LTP of field potentials in the ventral portion of the vestibular nucleus and LTD in the dorsal portion of the nucleus

[29]. The induction of LTP and LTD each require N-methyl-D-aspartate (NMDA) receptor activation [29,30], with additional regulation by metabotropic glutamate receptors [31–33].

The probability of evoking LTP and LTD in the vestibular nuclei is altered dramatically by both visual and vestibular experience. Visual experience is required for a developmental shift from LTD to LTP in the ventral vestibular nucleus [34]. Shortly after the onset of eye opening, brain slices obtained from rats kept in darkness tended to exhibit LTD after vestibular nerve stimulation. Exposure to light restored the probability of LTP induction that was observed in light reared animals. The developmental shift from LTD to LTP occurs concomitantly with a change in the ratio of mGluR1 and mGluR5 receptors [35], suggesting the interesting possibility that vision regulates expression of metabotropic glutamate receptors.

Head motion signals also regulate the probability of inducing synaptic plasticity in vestibular nerve field potential responses. Loss of vestibular function unilaterally (the vestibular equivalent of monocular deprivation) decreased the probability of evoking LTP in the ventral portion of the vestibular nucleus contralateral to the lesioned side. The same experimental manipulation decreases the probability of evoking LTD in the dorsal portion of the vestibular nucleus on the ipsilateral side [36]. A potential explanation for the shift in LTP and LTD probability derives from intriguing results demonstrating that peripheral vestibular dysfunction produces a marked downregulation of GABA and glycine receptor sensitivity in neurons of the vestibular nucleus [37–39]. Neither the mechanisms nor the functional significance of the experience-dependent shifts from LTD to LTP are known; neurons in the ventral portion of the vestibular nuclei tend to project to oculomotor nuclei and the spinal cord, whereas neurons in the dorsal vestibular nuclei tend to project intrinsically within the vestibular nuclear complex [40,41]. Mechanistic analyses at the cellular level are required to elucidate how visual and vestibular information affect synaptic plasticity and metaplasticity within specific populations of neurons of the vestibular nucleus.

Changes in neuronal excitability triggered by loss of vestibular drive

Neurons in the vestibular system fire at remarkably high rates in the intact animal, with resting rates on the order of 50–100 spikes/s and responses to head movements ranging up to 300 spikes/s. The high firing rates observed *in vivo* arise partially from the intrinsic pacemaking capabilities of neurons of the vestibular nucleus but are predominantly driven by excitatory synapses from vestibular nerve axons, which have resting firing rates of about 50–100 spikes/s. Loss of peripheral vestibular function silences the vestibular nerve, resulting in a significant

loss of spontaneous firing in neurons of the vestibular nucleus which then returns to control values within about a week, even in the absence of vestibular nerve recovery [42,43]. This robust plasticity almost certainly underlies the restoration of oculomotor and postural stability observed in humans and other species after vestibular dysfunction and, therefore, is of interest both clinically and as a model for deafferentation-induced central nervous system plasticity.

Electrophysiological recordings in brain slices obtained from labyrinthectomized animals (in which the vestibular periphery was ablated surgically) have provided considerable evidence that both synaptic and intrinsic plasticity contribute to the restoration of vestibular nucleus neuron activity [43]. Spontaneous firing rates of neurons of the vestibular nucleus *in vitro* increase by an average of 20% within four hours of labyrinthectomy, and remain elevated for at least one week (reviewed in [44]). The increases in firing rates require the cerebellar flocculus [45] and depend on glucocorticoid activation [46]. Interestingly, when synaptic transmission is blocked *in vitro*, the increases in spontaneous firing rate are only observed during the first 48 hours after labyrinthectomy [47], indicating that changes in baseline transmitter release or receptor sensitivity [37–39] might contribute to increased excitability at later times.

Intracellular recordings *in vitro* indicate that lesion-induced increases in neuronal excitability can persist for at least one month [48,49]. After one month, spontaneous firing rates obtained with sharp electrodes were not different from control rates, but responses to intracellular current injection with ramp or sinusoidal stimuli in slices from lesioned animals were stronger, both on the ipsilateral [48] and on the contralateral side [49], than those in a control set of slices. Interestingly, the distribution of afterhyperpolarization (AHP) profiles was differentially affected on the two sides: neurons ipsilateral to the lesion tended to have deeper AHPs, whereas neurons on the contralateral side tended to have shallower AHPs [49]. These findings provide evidence that intrinsic conductances that govern the action potential are regulated by experience.

Intrinsic plasticity in the vestibular nuclei

A novel form of activity-dependent plasticity of intrinsic excitability described recently in neurons of the vestibular nucleus could potentially contribute either to adaptive changes in vestibular function during recovery from peripheral damage or to oculomotor learning in intact animals [50]. In spontaneously firing neurons of the vestibular nucleus recorded in brain slices, brief periods of synaptic inhibition or membrane hyperpolarization produce a dramatic increase in both spontaneous firing rate and firing responses to intracellularly injected current (Figure 1). These increases in excitability, termed ‘firing

rate potentiation’ are accompanied by reductions in the AHP and increases in input resistance. Reductions in the sensitivity to the specific channel blocker iberiotoxin indicate that the expression of firing rate potentiation involves reductions in BK type calcium-activated potassium currents [51], which normally oppose excitability and contribute to the AHP [50].

The mechanisms that induce firing rate potentiation differ substantially from other forms of synaptic or intrinsic plasticity studied to date. A wealth of previous studies in other neurons have led to the commonly accepted tenet that cellular plasticity is triggered by increases in intracellular calcium levels. Firing rate potentiation, by contrast, is triggered by decreases in intracellular calcium levels, which in turn reduce tonic activity of calcium/calmodulin-dependent protein kinase II (CaMKII) [52]. In spontaneously firing vestibular nucleus neurons, CaMKII activity is maintained at near maximal levels by calcium influx that occurs with each action potential: decreases in CaMKII activity oppose excitability by reducing BK currents. This unusual form of plasticity might be common to spontaneously active neurons throughout the brain, and would not have been observed in typical plasticity studies that clamp membrane potential below spike threshold.

Conclusions

The vestibulo-ocular reflex has long held promise of being a system that is amenable to integrated, mechanistic analyses of experience-dependent plasticity from the behavioral through the cellular and molecular levels. A plethora of candidate cellular forms of plasticity identified in the vestibular nuclei could mediate oculomotor learning and compensation for dysfunction in the VOR. Relating these cellular properties to their behavioral consequence, however, requires knowing the identity and function of the cell types recorded *in vitro*.

Expression of cellular plasticity is diverse among the heterogeneous pool of neurons of the vestibular nucleus [48–50,53], making it particularly compelling to probe the functional identity of recorded neurons. As such, researchers have begun to develop methods for classifying neurons of the vestibular nucleus recorded *in vitro*. Single cell polymerase chain reaction (PCR) in conjunction with whole cell patch recording has elucidated the AHP profiles of glutamatergic and GABAergic neurons [54], and targeting of retrogradely labeled neurons has identified the physiological phenotype of neurons of the vestibular nucleus that project to the oculomotor nuclei [55]. Analyses of AHP profiles indicate that the vestibular nuclei contain two predominant classes of neurons [44] that are differentially contacted by glycinergic and gabaergic synaptic terminals [56]. A transgenic mouse expressing green fluorescent protein (GFP) in Purkinje cells has revealed that flocculus target neurons in the

vestibular nuclei have physiological properties that are unique among neurons of the vestibular nucleus but remarkably similar to those of Purkinje cell targets in the deep cerebellar nuclei [57]. These studies set the stage for understanding how cellular mechanisms of plasticity operate within the context of a diverse population of spontaneously firing neurons of the vestibular nucleus to produce adaptive changes in behavior.

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