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Interactive report

Vestibular efferent neurons project to the flocculus[1]

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Abstract

A bilateral projection from the vestibular efferent neurons, located dorsal to the genu of the facial nerve, to the cerebellar flocculus and ventral paraflocculus was demonstrated. Efferent neurons were double-labeled by the unilateral injections of separate retrograde tracers into the labyrinth and into the floccular and ventral parafloccular lobules. Efferent neurons were found with double retrograde tracer labeling both ipsilateral and contralateral to the sites of injection. No double labeling was found when using a fluorescent tracer with non-fluorescent tracers such as horseradish peroxidase (HRP) or biotinylated dextran amine (BDA), but large percentages of efferent neurons were found to be double labeled when using two fluorescent substances including: fluorogold, microruby dextran amine, or rhodamine labeled latex beads. These data suggest a potential role for vestibular efferent neurons in modulating the dynamics of the vestibulo-ocular reflex (VOR) during normal and adaptive conditions.

Theme: Motor systems and sensorimotor integration

Topic: Vestibular system

Keywords: Gerbil; HRP; BDA; Fluorogold; Fluorescent beads; Vestibular efferent neurons; Motor control

1. Introduction

Hair cells in the peripheral vestibular neuroepithelium form synaptic connections with both afferent and efferent fibers from the central nervous system [33]. The source of these efferent connections in the gerbil cristae ampullares and otolith organs are from somata located bilaterally in the brainstem just dorsal and ventral to the genu of the seventh nerve and interposed between the abducens and superior vestibular nuclei [27]. In addition to their projection to the labyrinth, collateral projections of the efferent nerve bundle have been found to project to the interstitial nucleus of the vestibular nerve root [27]. Widespread terminal fields in the labyrinth characterize the peripheral innervation by individual efferent fibers, which contrast with the restricted pattern of single primary afferent innervation [28].

Retrograde labeling studies in different species [6,7,16,18,31,34] indicate that the flocculus receives significant afferent projections arising bilaterally from the vestibular nuclear complex including the medial, superior, and inferior vestibular nuclei, the y group nuclei, as well as the interstitial nucleus of the vestibular nerve. A small percentage, typically less than 15%, of vestibular primary afferent neurons were found to project directly to the flocculus [4–6,25,26]. Floccular projecting afferent neurons also arise from the perihypoglossal, paramedian reticular, and basilar pontine nuclei; the nucleus reticularis tegmenti pontis; areas within the medial longitudinal fasiculus; the contralateral inferior olive via the dorsal cap of Kooy; as well as from several cranial motor nuclei including the abducens, facial, and ambiguous nuclei [5,6,18,25,26,31]. Additionally, several afferent labeling studies of the flocculus in monkey, cat, rat, and gerbil [16,18,26,31] have described supragenual labeling in and near the region corresponding to the location of the vestibular efferent ‘group e’ in the squirrel monkey [10].

The above studies provided evidence of retrograde labeling of both brainstem flocculus projecting neurons (FPNs) as well as direct primary vestibular afferent input to the flocculus. These converging elements have been proposed to contribute to vestibulo-ocular gain adaptation [15] in what Lisberger et al. defined as a modifiable

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vestibulo-ocular pathway, dominated by inputs from low gain, regularly firing canalicular vestibular primary afferent neurons [29]. Additionally, those inputs associated with the unmodifiable pathway are relayed through the vestibular brainstem nuclei [19,22].

The purpose of the present study was to determine the existence of collateral projections from both ipsilaterally and contralaterally located vestibular efferent neurons to the cerebellar cortex, in particular, the flocculus and ventral paraflocculus. The findings suggest a reinterpretation of how efferent neurons might influence the vestibulo-ocular reflex during active head movement or under different states of arousal. Some of the data presented have been published previously in abstract form [30].

2. Materials and methods

Data were obtained from 52 gerbils (*Meriones unguiculatus*) of both sexes weighing between 48 and 82 g used in the present study. Under general anesthesia (Nembutal (sodium pentobarbital) and ketamine, each 40 mg/kg), the gerbils were placed into a Kopf stereotaxic frame and maintained at about 37°C. Using aseptic technique, a post-auricular approach through the thin bulla was used to expose both a window over the lateral surface of the paraflocculus for the injection of the flocculus, and a window over the sensory neuroepithelium of the vestibular labyrinth. A series of simultaneous injections were made into the flocculus and vestibular sensory neuroepithelium using a combination of neuronal tracers (Table 1). After a given period to allow neuronal tracer uptake, animals were deeply anesthetized using 17% intraperitoneal chloral hydrate (1.0 ml) or urethane (0.7 ml, 500 mg/kg), then perfused with 3 to 4% paraformaldehyde in 0.1 M phosphate buffered saline (PBS). The brain tissue was removed, cryoprotected in 20% sucrose, and frozen sectioned at 40 μm. Further histological processing was then performed related to the combinations of neuronal tracers used.

Horseradish peroxidase (HRP): using an approach through the bulla of the middle ear cavity in 12 animals, 10% HRP in 0.05 M Tris buffer was unilaterally injected into the flocculus or into the sensory neuroepithelium of the labyrinth [27]. At a given site of injection, HRP was delivered in a total volume of 200 to 500 nl or delivered ionophoretically with 5 μA of positive current for 5–15 min. After a 2–3-day survival time the animals were anesthetized and perfused as described above. The tissue, once removed, was then quenched in alcohols to remove endogenous peroxidase activity from remaining blood cells, and rinsed in a solution of cobalt chloride in Tris buffer (pH 7.6). The tissue was then reacted with a diaminobenzidine (DAB), nickel ammonium sulfate solution (the nickel and cobalt intensifications were omitted for some animals to facilitate visualization of fluorescent tracers), with H_2O_2 or glucose oxidase as an oxygen donor to precipitate a black reaction product in labeled neurons.

Biotinylated dextran amine (10,000 M_w BDA Sigma): in six animals, unilateral injections of BDA were made into the flocculus or sensory neuroepithelium. A glass pipette (20 μm tip) filled with a solution of 10% BDA in phosphate buffered saline (PBS, 0.01 M, pH 7.4) was placed stereotaxically into the flocculus of the cerebellum, ~1.4 to 1.5 mm from the surface of the paraflocular exposure window at an angle of 45° pitch and yaw. BDA was injected ionophoretically by passing direct positive anodal current, 5 μA, for 10 min. After a survival of 10 to 12 days, the animal was anesthetized and perfused as described above. The tissue was then incubated following the protocol for avidin–biotin peroxidase procedure (Vector Labs) using a cobalt intensified diaminobenzidine/glucose oxidase reaction [1,17]. Sections were then rinsed again in PBS, mounted on subbed slides, and coverslipped with Permount.

Fluorescent tracers (red and green rhodamine beads, microruby dextran amine (MDA), and fluorogold (FG)): all animals had at least one fluorescent tracer and most (n= 34) had two injected simultaneously in the flocculus and sensory neuroepithelium. Fluorescent tracers were pressure injected into the respective region of interest, and were processed according to the non-fluorescent tracer protocols when such tracer was present. A precaution to minimize exposure to alcohols and xylenes when processing all fluorescent tracers was also followed. When using 0.03 μm latex microspheres (LumaFlur, Inc.) with red and green rhodamine fluorophore, a glass pipette (20 μm tip) was used for delivery of 400 to 700 nl to the flocculus, or 200 to over 1000 nl in the sensory neuroepithelium. Microruby dextran amine, 3000 M_w Dextran Rhodamine (Molecular Probes), was used as a 10% solution in 0.01 M phosphate buffer, 250 nl injected into the flocculus and from 200 to 350 nl into the sensory neuroepithelium. And finally, a 3% fluorogold (Fluorochrome, Inc. and Molecular Probes) solution was injected into the flocculus (100 to 500 nl) and into the sensory neuroepithelium (250 to 500 nl). Survival times are listed in Table 1.

Table 1
Neuronal tracer combinations used to double label vestibular efferents projecting to the flocculus or paraflocculus

Floccular label	Epithelial label	*N*	Survival time
BDA	Fluorogold	1	10–12 days
Rhodamine beads	BDA	2	10–12 days
Rhodamine beads	HRP	8	2–3 days
Fluorogold	BDA	3	10–12 days
Fluorogold	Green rhodamine	2	5 days
Fluorogold	Microruby dextran	8	9–14 days
Fluorogold	Rhodamine beads	21	3–14 days (8±3)
HRP	Fluorogold	4	2–3 days
Microruby dextran	Fluorogold	3	8–9 days

3. Results

Injections of fluorescent tracers in combination with either BDA or HRP ($n=18$) failed to produce double labeling, but resulted in interspersed labeling with different tracers in neighboring cells. The floccular and ventral paraflocculus injections of retrograde tracer resulted in extensive bilateral labeling of the dorsal group of efferent neurons (Fig. 1, FG). These cells are small to medium sized (average cross-sectional area=42 μm) fusiform neurons organized in a dense cluster at the dorsal and dorsolateral edge of the genu of the facial nerve. There were no apparent differences found in the number of labeled floccular projecting neurons in the region of group e ipsilateral and contralateral to the floccular injection site in this study.

Retrograde tracer labeling of FPNs in the gerbil revealed an extensive brainstem pattern of distribution (Fig. 2). Medial to the genu, a small number of cells were labeled bilaterally within the borders of the abducens nucleus. In addition to this labeling, we observed cells, bilaterally, in the prepositus hypoglossi, nucleus ambiguous, raphe magnus, raphe pallidus, locus coeruleus, solitary nucleus, the interstitial cells of the medial longitudinal fasciculus, and in the pontine and paramedian raphe, and reticulotegmental nuclei. Retrogradely labeled cells were also found bilaterally in the interstitial nucleus of the vestibular nerve root, which is the only previously recognized site in the CNS to receive input from the vestibular efferents [27]. Bilateral labeling, although stronger ipsilaterally, was observed in the medial, lateral, superior and inferior vestibular nuclei, Roller's nucleus, and nucleus Y. We also routinely observed a dense cluster of cells labeled in the ventromedial medial vestibular nucleus. In the contralateral inferior olivary nucleus, labeling was found in the dorsal cap, ventral lateral outgrowth, and ventromedial medial subnuclei.

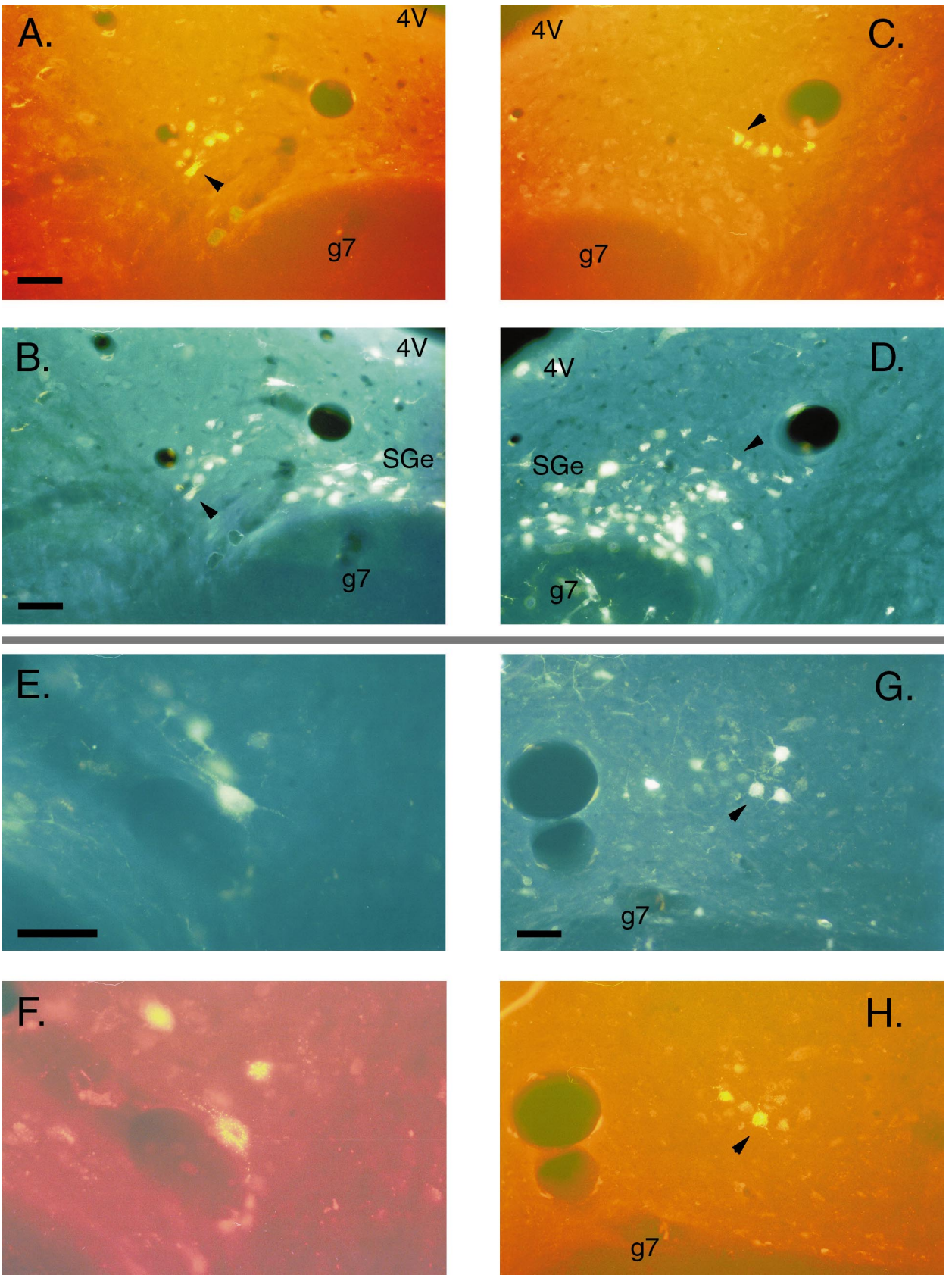
Simultaneous injection of two fluorescent neuronal tracers separately into the flocculus/ventral paraflocculus and the vestibular sensory neuroepithelium ($n=34$) produced successful double labeling by both tracers. Two successful combinations included: (1) rhodamine and fluorogold, labeled 47.8% ($n=11$) with labeling failure occurring only with rhodamine uptake, (2) microruby dextran amine and fluorogold, 100% ($n=11$). Thus, double labeling occurred in 22 animals, or 72.7% ($n=16$) of those 34 simultaneously injected with fluorescent tracers (Fig. 1). Occasionally labeling was sparse ($n=4$ with two using rhodamine and two microruby dextran amine) producing double-labeled cells in only 2 to 7 cells in cases where 48±45 efferent neurons were labeled (less than 1% double labelling of efferents, Fig. 1E–H). However, the remainder of successfully labeled animals displayed more robust double labeling (20 to 128 cells, average of 65) and a much larger percentage of efferent neurons with double labeling (60.5%, Fig. 1A–D). There were no apparent statistically significant differences in bilateral distribution of the double labeling of efferents; however, there was slight but consistent ipsilateral dominance (42.7% of efferent neurons double labeled ipsilateral to the injected flocculus (13.7±14.4) of (32.1±20.3) efferent neurons, and 35.9% contralateral (10.8±11.2) of (30.1±16.5)).

4. Discussion

Our findings show extensive distributions of retrograde labeled FPNs in arousal, autonomic, and vestibular brainstem pathways. Vestibular efferent neurons labeled by neuronal tracer from the vestibular sensory neuroepithelium were also found to be double labeled as FPNs. This indicates that the vestibular efferent neurons project to hair cells of the vestibular sensory neuroepithelium and to the interstitial nucleus of the vestibular nerve root [27], as well as to the flocculus and/or ventral paraflocculus.

The efferent projections to the labyrinth display a complimentary distribution, with efferent neurons ipsilateral to the vestibular canal predominantly projecting to the central zone of the cristae, and the contralateral efferent neurons predominantly projecting to the planum and peripheral zones [28]. Evidence from the chinchilla and monkey suggest that irregularly firing afferents arise from the central zones and more regularly firing afferents are distributed in the outer or more peripheral zones of the cristae [3,8,23] (see Fig. 3). Physiological evidence has been presented in other investigations to implicate the efferent system in modification of vestibular afferent discharge and the dynamic responses of irregularly discharging first order neurons [10,13]. It has been speculated that efferent neurons could provide a means for improving afferent response linearity by increasing afferent firing rates and reducing vestibular gains [10]. The resulting implication is that such modifications may be necessary during intentional and high acceleration head movements

Fig. 1. Demonstration of double labeling of efferent neurons labeled by red rhodamine beads from the vestibular periphery and fluorogold from the flocculus and ventral paraflocculus. (A) through (D) were taken from one animal and (E) through (H) from another. (A), (C), (F), and (H) display rhodamine labeling, while (B), (D), (E), and (G) show fluorogold. (A) and (B) contain double labeled cells contralateral to the site of injection and (C) and (D) contain double labeling ipsilateral to the injection site (example cells displaying double label are indicated with green arrow heads). All bars shown in (A), (B), (E), and (G) are 250 μm in length. As noted by the size of the 250 μm bar in (E), higher magnification allowed the determination of double labeling from the stippled label which can be seen in neural soma and processes in (E) and (F). Comparing (G) and (H) to the labeling seen in (A), (B), (C), and (D) demonstrates the range in the degree of labeling seen across animals. g7, genu of the facial nucleus; 4v, fourth ventricle; SGe, supragenual nucleus.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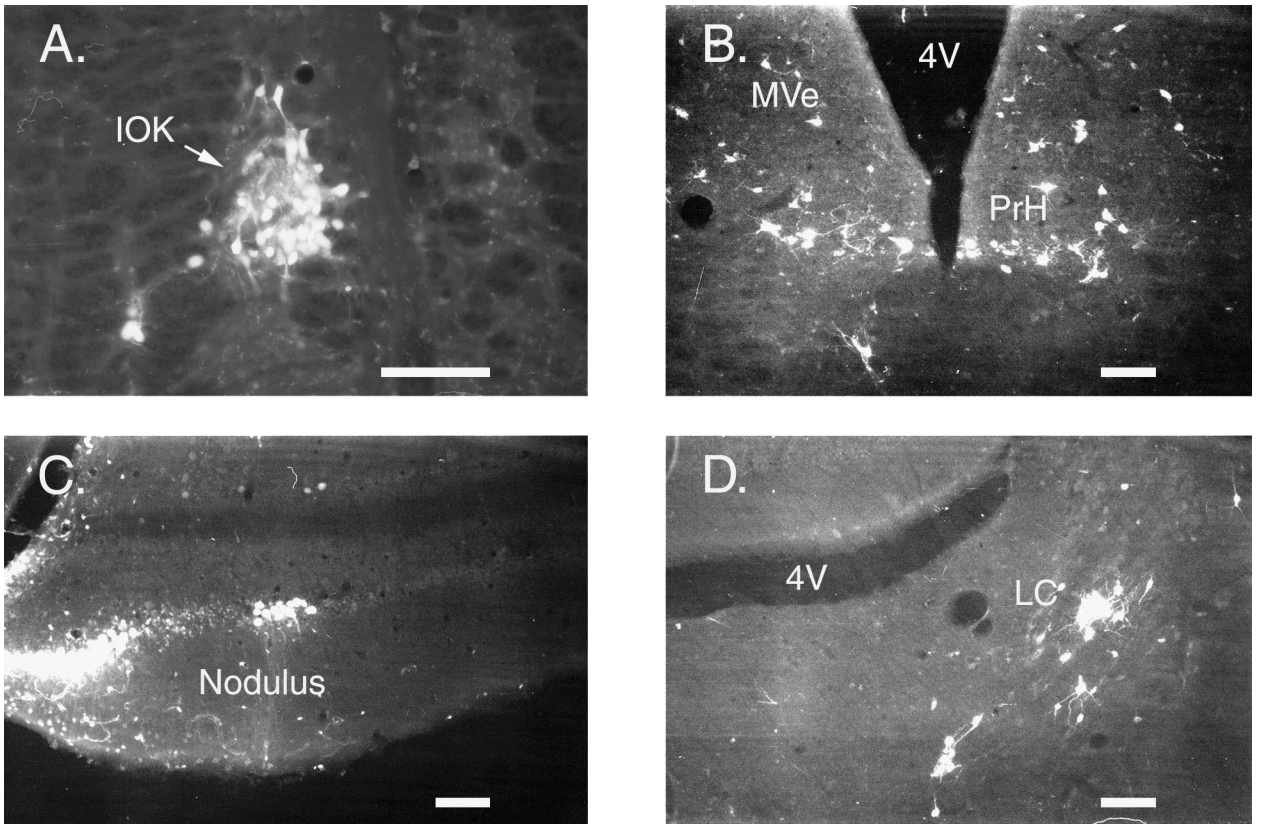

Fig. 2. Examples of retrograde labeling from the flocculus in the (A) cap of Kooy of the inferior olive (IOK), (B) prepositus hypoglossi (PrH) and medial vestibular nucleus (MVe), (C) nodulus of the cerebellum, and (D) locus coeruleus (LC). Reference bar is 500 μm.

to improve the response of vestibular afferents by reducing rectification or silencing.

Vestibular afferent projections to the gerbil flocculus were found to be exclusively from dimorphic type afferents innervating the peripheral zones of the anterior, posterior, and horizontal semicircular canal cristae [29]. Such afferent neurons innervating those areas were predominantly regularly firing afferents with lower to intermediate vestibular gain in the chinchilla [3,12]. Since the vestibular efferents influence the linearity of responses predominantly in irregularly firing afferents through shifts in dynamic response gains and firing rate, there may be a subsequent imbalance in the responses of central vestibular neurons. This imbalance would be found between neurons that receive a dominantly irregular afferent contribution versus those that receive dominantly regularly firing

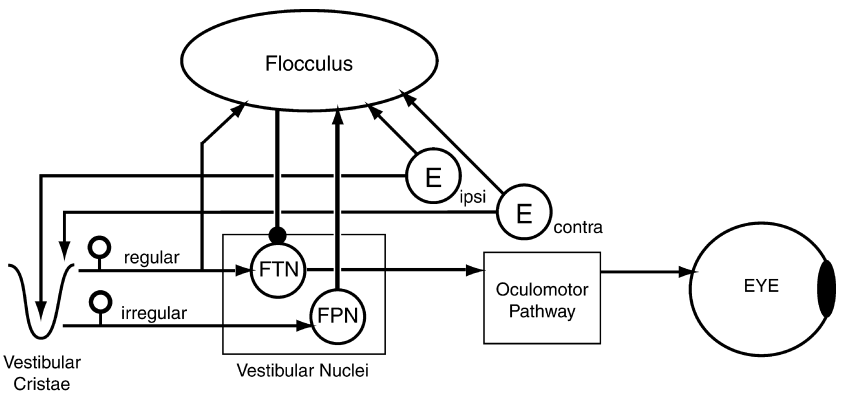

Fig. 3. (A) Diagram of predominant projections from the vestibular efferent neurons to the vestibular cristae, and from the vestibular cristae to the flocculus. (B) Diagram of connectivity from the vestibular canal demonstrating the imbalance of efferent influences in the vestibular nuclei when the dominant physiological effect of efferent activity is found in high gain, irregularly firing afferents. The floccular target neurons receive low gain, regular afferent input and input from the flocculus, which receives direct afferent input only from low gain, regularly firing afferents. Efferent neuron projections to the flocculus allow a possible physiological influence not seen in regular afferent input alone.

afferent input. For example, vestibulo-ocular neurons are thought to receive a proportionally greater input from low gain, regularly discharging primary afferents [11]. In contrast, secondary neurons projecting to the flocculus display significantly more irregularly firing input [14]. It can therefore be argued that the vestibulo-ocular pathways are dominated by regularly firing afferent inputs. This is connected with the finding that functional ablation of irregular afferents does not alter the vestibulo-ocular reflex to head rotations except at low frequencies or during constant velocity rotations [2,24]. Flocculus target neurons, as part of the vestibulo-ocular pathway, are thought to be innervated by regularly firing input because they possess longer latencies suggestive of the lower conduction velocities of the regularly firing afferents and because of their putative involvement in the vestibulo-ocular pathway [20] (see Fig. 3). Varying the proportions of the irregular and regular afferent signal input could be significant for maintaining appropriate signal processing across a wide range of stimuli. Further, the ratios of the type of afferent signal could also be important for maintaining proper response calibration [9]. Although much of the vestibular pathway physiology outlined in the above discussion is from squirrel monkey, the generalization to the gerbil, with known anatomical differentiation of afferent projections, may be useful for assessment of the functional significance of the novel efferent projections.

The collateral projections of the vestibular efferents to the flocculus and ventral paraflocculus of the cerebellum also suggests that those neurons may directly influence cerebellar cortex that is involved in the regulation and adaptation of the vestibulo-ocular reflex. Reduction of errors in the vestibulo-ocular reflex resulting in retinal slip is produced by plasticity of Purkinje cells of the flocculus [15]. Further refinement of the theory regarding the role of vestibular brainstem and cerebellar plasticity during vestibular adaptation resulted in defining multiple modifiable and non-modifiable pathways through the vestibular system [20]. Initial findings of Fos expression in the gerbil during vestibular adaptation support the more distributed view of adaptation plasticity [32]. The modifiable pathways proposed by Lisberger involve flocculus target neurons, which are dominated by regularly firing afferents [21], and thus provide interaction with vestibular efferents principally through the flocculus. Thus arousal, attentional, or autonomic influences on vestibular efferents could act to modulate the saliency or significance of vestibular input in the modifiable pathways in the short-term and vestibulocerebellar processing in the modifiable pathway during the learning process over the long-term.

Our findings suggest that vestibular efferent neurons project collaterals to the flocculus and ventral paraflocculus bilaterally, as well as the vestibular sensory neuroepithelium. Such novel projections, extending the influence of the vestibular efferent neurons and viewed in light of the anatomical input to those neurons and the differential physiological output to the vestibular neuroepithelium, could represent a sensory balancing or homeostatic mechanism.

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