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Review

Fos expression in the vestibular brainstem: What one marker can tell us about the network

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Abstract

Fos inducible transcription factor expression in rodent brains (rats and gerbils) during manipulations of vestibular input is reviewed. Stimuli included centripetal hypergravity, unilateral labyrinth lesion or semicircular canal plugging, rotational axis cross-coupling (Coriolis forces), high and low rotational vestibulo-ocular reflex gain adaptation, translabyrinth galvanic stimulation, pharmacological manipulation, and combinations thereof. Each type of stimulation elicited unique but partially redundant response patterns in the vestibulo-olivo-cerebellar (VOC) network that reflect the origin and interaction of the labyrinth inputs. On the basis of these patterns, a trained observer can predict what the animal experienced during testing; the patterns of VOC Fos expression reveal a trace of recent genomic activity. Based on principal component analysis, VOC network modules associated with lesion recovery, spatial representation and the calibration of gravity, and optokinetic influences are proposed. Probable and possible gene targets of the Fos protein are also reviewed.

Theme: Sensory systems
Topic: Auditory, vestibular, and lateral line

Keywords: c-*fos*; Inducible transcription factor; Immediate early gene; Plasticity; Rodent; Rat; Gerbil; Neural network; Gravity; Coriolis; Ketamine

Contents

1. Introduction

Within a narrow non-lethal range of environmental changes or sensory pathology, the nervous system has a remarkable ability to adjust its network to retain function in a new situation. The cellular and molecular basis of this adaptive capacity is the subject of many neuroscience studies. The recognition of genomic mechanisms controlling these changes entices us with a molecule-to-behavior scaffold of understanding. Brainstem networks process well-defined sensory modalities and are simpler compared to their cortical descendents. The geometrical nature of vestibular inputs in particular (head rotation, position, and translation) and an easily measured output (eye movement) make this system attractive for studying neural adaptation.

The vestibulo-olivo-cerebellar (VOC) network is a well-studied circuitry of bilateral synaptically related neurons that influence each other and receive vestibular labyrinth and multiple sensory inputs [3]. This review will focus on the VOC and expression of the inducible gene regulatory transcription factor protein, Fos [37], during many types of challenging new environments that require network change. Although the VOC itself is reciprocally

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connected to myriad other brain systems, it is these neurons that carry vestibular signals and are within three synapses of their source and can be shown to depend on a functional labyrinth for Fos expression [46].

While the vestibular system in general must coordinate a host of head inertia responsibilities, the vestibulo-ocular reflex (VOR) in particular is a highly conserved bilateral system for stabilizing visual input. In most animals, a high frequency rotational mechanism (semicircular canals, RVOR) contributes to retinal stability in conjunction with a low frequency translational (otolith, TVOR) and visual (optokinetic) assist. The basic anatomical pathways are known. The RVOR can be as simple as a three-neuron chain: sensory afferent, vestibular, and oculomotor neurons. The TVOR pathways are more polysynaptic for computational reasons [2]. Four basic functional cell types have been identified in the vestibular nuclei: position-vestibular-pause, burst-position, eye-head, and vestibular-only neurons, which differ in their responses and response polarity to head and eye movements [2,53,76]. Neuronal responses to vestibular inputs and training have been investigated, the role of each area has been explored, and some agreement has been reached as to their individual function. For example, the cerebellar flocculus is now well accepted as an important part of horizontal VOR gain adaptation [38,59]. Floccular target neurons (FTNs) are a subpopulation of vestibular nucleus neurons that receive direct inhibitory Purkinje cell projections from the cerebellum and are thought to be one physical site of adaptive changes. In contrast, floccular projecting neurons (FPNs) are a separate subpopulation of vestibular neurons that can influence floccular responses. In non-foveated animals, visual information reaches the vestibular system via retinal slip information, generating the optokinetic reflex (OKR), one type of slow eye movement [40]. Optokinetic signals passing through the accessory optic system reach the prepositus and vestibular nuclei, the cerebellum via mossy fibers, and the powerful climbing fibers of the inferior olivary dorsal cap which project contralaterally onto modular cerebellar networks of Purkinje cells. Therefore, another site of plasticity is the vestibulocerebellum, specifically Purkinje cells that can act as comparators of intended and actual movement. A long literature deals with the arguments for different sites of VOR plasticity (reviewed in [5]). Different ocular kinematics are required when a fovea is present. The optokinetic reflex [58] is supplemented by other visuomotor and target following reflexes (ocular following reflex, smooth pursuit) requiring cerebral cortical inputs. The VOR in three dimensions reflects both canal and otolith inputs and continues to be modeled [73]. A tightly coupled triad of sensory control and feedback therefore exists between the vestibular nuclei, inferior olive, and vestibulocerebellum.

However, understanding the basic anatomy and function of vestibular neurons does not necessarily tell us very much about how the same system responds to functional challenges. VOR reflexes are adaptable quickly with visual/head mismatch paradigms (minutes) and in both directions (high or low), but the mechanism of each gain direction apparently differs [25,79]. Adaptation depends on an intact inferior olivary nucleus, which provides corrective signals to cerebellar networks [83]. The sensorimotor brain is highly interconnected and can meld inputs of all kinds to extract behavioral responses. The brain is opportunistic and redundant in the sense of using whatever sensory or efference modality is present [5,7,78]. For example, optokinetic signals share at least some penultimate pathways prior to oculomotor neurons [58]. Recent models propose such combinations by using coordinate transformation of canal signals from a head-fixed to a spatial reference frame [33]. Vestibular cortical projections likely have important roles to play in perception and navigation [17,22,88]. Furthermore, there is good evidence that the brain can maintain multiple functional states or response patterns, as demonstrated by context-specific VOR gain adaptation [77] and yaw and pitch cross-axis adaptation [70]. Such adaptation appears to be constrained by the complexity of the adaptation task [86]; see also [51]. Many studies have now shown that there exists a complex interplay of stimulus direction, habituation, and adaptation in the VOR [12]. Recent evidence also supports the existence of multiple cellular mechanisms of VOR plasticity which operate over distinct time courses [27,79].

Fig. 1 outlines a three-dimensional dorsally oriented coronal view of the rodent VOC network in situ and serves as a guide for the simpler representations in Fig. 2. Furthermore, representative Fos immunolabeling in VOC neurons following hemilabyrinthectomy–a peripheral loss of vestibular input unilaterally–is shown within the regions [10,45,52,54,78]. Large (red) dots represent Purkinje cells in the ventral paraflocculus, and other dots represent other neurons of mixed types. Each letter in the abbreviation VOC represents a module of a triad: (1) *v*estibular nuclei complex, (2) inferior *o*livary complex, and (3) vestibular (posterior) *c*erebellum. These three modules are heavily interconnected with both excitatory and inhibitory projections in specific pathways, as well as commissural crossing. Each module has subregions and unique populations of cell types with special roles [89]. For example, vestibular primary afferent neurons are excitatory and reach, on the same side, both the vestibular nuclei and the vestibulocerebellum at granule cells. The cerebellar Purkinje cells form the only output of the cerebellum and send inhibitory projections ipsilaterally to the deep cerebellar nuclei and vestibular complex. The vestibular and inferior olivary complexes exchange reciprocal projections that are both crossed and uncrossed, excitatory and inhibitory [3]. And, the inferior olive projects slowly firing and powerful excitatory climbing fibers contralaterally to the Purkinje cells.

These anatomical relationships only begin to frame the network. Both the instantaneous firing rate and firing