Impaired Perception of Gravity Leads to Altered Head Direction Signals: What Can We Learn From Vestibular-Deficient Mice?

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Beraneck M, Lambert FM. Impaired perception of gravity leads to altered head direction signals: what can we learn from vestibular-deficient mice? J Neurophysiol 102: 12–14, 2009. First published May 20, 2009; doi:10.1152/jn.00351.2009. Many mutant mouse strains display pathological behaviors, such as head tilts, head bobbing, or circling and waltzing, strongly suggesting that their vestibular system is impaired. Recently, Yoder and Taube studied head direction signals in tilted mutant mice, which have an impaired gravitation sensitivity in the vestibular periphery. Here we summarize their findings and discuss a caveat related to the general use of mutant mouse strains in systems physiology.

The vestibular sense organs located in the inner ear consist of semicircular canals, which are sensitive to head rotation, and of otolith organs, which sense linear acceleration and the position of the head relative to gravity. Accordingly, the otolith organs are essential for the translation of the body position and relative movements into an earth-centered reference frame (Angelaki and Cullen 2008). Head acceleration is transduced into neural signals by hair cells and transmitted through afferent fibers in the VIIIth nerve to central vestibular neurons in the brain stem (Fig. 1A). By integrating vestibular signals and other internal information (proprioceptive and motor cues) with external sensory stimuli (visual, olfactory), the brain computes the position and direction of the head/body in space. Notably, head position and direction are encoded by distinct, interconnected groups of neurons in the limbic system (see Fig. 1A) (Taube 2007). Most of what we know about head direction signals is from experiments conducted in the adult rat. Although little is known about the mouse head direction (HD) signals, Yoder and Taube (2009) recently recorded neurons located in the anterodorsal thalamus (ADN) of wild-type or vestibular-deficient mutant mice.

Yoder and Taube (2009) show that, compared with the ADN HD cells recorded in rats, the basic properties of the respective cells in wild-type mice show smaller directional information content (bits) with less accurate and robust perception of HD signals over time. The observed differences between the two species could originate in the mouse’s lower visual acuity and impaired velocity storage. However, a mutually nonexclusive possibility is that the lower HD accuracy partly reflects the dynamics of vestibular information processing in mice. Indeed, recent work on vestibular nerve afferents (Yang and Hullar 2007) and on central vestibular neurons (Beraneck and Cullen 2007) in wild-type mice suggested that the information content of vestibular sensory signals is lower than that in other animals, including rats. Given the importance of vestibular inputs in path integration, it is likely that more limited vestibular information contents cause less accurate and less robust HD signals in mice. Furthermore, the mice tested were untrained and did not have to reach a specific goal during the experiment. The experimental conditions therefore generated low attentional demand and cognitive effort, previously related to instability in the hippocampal spatial representation of mice (Kentros et al. 2004).

Lesion experiments specifically targeting the semicircular canals, but not the otolith organs, previously demonstrated in mature rats that semicircular canal–related signals are involved in the generation of HD signals (Brown et al. 2006; Muir et al. 2004; Stackman and Taube 1997). For anatomical reasons, a similar approach (i.e., a specific lesion of the otolith organs) cannot be performed. To bypass this difficulty, Yoder and Taube (2009) used a strain of vestibular-deficient mice. In these mice, the dense mineral deposit (otoconia), which covers the epithelium of the otolith organs and is essential for the transformation of the sensory stimulus by the mechanoreceptors in the epithelium, is absent. These mutants are often referred to as “tilted” because they suffer from a slight postural deficit (Fig. 1B). They are not able to swim and become imbalanced when challenged (Zhao et al. 2008), but notably show no disoriented phenotype (see Fig. 6C and related text in Yoder and Taube 2009). Since recording HD cells in tilted mutant mice was much more difficult than that in wild-type, Yoder and Taube (2009) found fewer HD cells (~50%) with considerably lower directional tuning (Fig. 1B). In almost all tilted mice a specific pattern of activity that consisted of random, nonperiodic bursts of activity was encountered (see Fig. 4C in Yoder and Taube 2009). The main conclusion of their comparison of wild-type and tilted mice was that signals from the otolith organs are critical for the maintenance of robust HD signals.

There is however, a caveat to be considered in the interpretation of these findings. The otoconia agenesis affects the functionally appropriate assembly of vestibular signal pathways and the known interaction between semicircular canal and otolith signals (Angelaki and Cullen 2008) in central vestibular neurons during the critical periods of the ontogeny (D. Eugène, S. Deforges, N. Vibert, and P.-P. Vidal, unpublished data; see also Sajdel-Sulkowska 2008 for a discussion). In fact, semicircular canal and otolith signals converge in roughly 50% of the central vestibular neurons (Straka and Dieringer 2004). Consequently, impaired otolith signaling leads to impaired processing of both spatial and dynamic aspects of all signals from the vestibular periphery. Harrod and Baker (2003) showed that the canal-driven eye movement responses of head tilt mice have a lower gain (Fig. 1, B1 and B2) and an abnormal timing during head rotation in the horizontal and vertical planes. Therefore the absence of oto-
related signals likely also leads to abnormal maturation of semicircular canal–related responses. In fact, it has been suggested that otolith-driven responses in vestibular circuits serve as a spatial reference frame for the canal-driven responses during early development (Lambert et al. 2008). While interpreting Yoder and Taube’s results, one has to consider that altered signaling of HD cells in tilted mice might not be solely related to the absence of the otoconia. Instead, it could be that an impairment of angular head acceleration signals in central vestibular neurons, related to the absence of a discharge modulation in afferent fibers from the otolith organs in these mice, plays a substantial role in the putative perceptual disorientation of tilted mice.

As shown by the work of Yoder and Taube, the use of mutant mice has many advantages for research in systems physiology. It nevertheless also raises questions about how the mutation alters the development and subsequently the physiology of the mature mutant animal. For example, the complete surgical removal of all vestibular end organs in wild-type adults results in transitory postural and locomotor deficits, including circling, that partially recover due to postlesional plasticity (see Curthoys 2000 for a review). On the other hand, the congenital absence of all vestibular inputs in another mutant strain (IsK) leads to a strikingly impaired locomotor behavior characterized by high-speed circling (Vidal et al. 2004; Eugène et al., unpublished data; see Supplemental Movie S1 for a comparison of the locomotor behavior of IsK and Tilt mutants1). Notably, unlike what happens after bilateral surgical removal of the vestibular end organs in adult animals, the behavioral deficits in IsK mutant mice are permanent. Together with the deficits in the IsK mutant mice, results from the work of Yoder and Taube show that the presence of fully functional vestibular organs during critical periods of development is instrumental for the establishment of proper locomotor and navigation capacities (Sajdel-Sulkowska 2008; Eugène et al., unpublished data).

Despite the physiological differences between wild-type and mutant mice, the technically challenging path taken by Yoder and Taube (2009) in switching from rat to mouse opens promising new perspectives for studying the neural substrates responsible for navigation not only in normal but also in genetically engineered mice. Where does this lead us? First, future experiments on HD neurons in wild-type mice could further investigate the role of attention in the maintenance of HD signals. As shown in the hippocampus, it would be interesting to know whether HD neurons in the ADN also show more robust responses when the environment is more behaviorally relevant (Kentros et al. 2004). This is a first step in

1 The online version of this article contains supplemental data.
understanding how idiothetic cues, such as vestibular signals, are used to navigate in the environment.

Second, we also need to better understand how vestibular information is processed at the level of the brain stem. What kind of information about head movements is implemented at the level of the vestibular nuclei and thus available for higher cognitive functions (e.g., path integration used during navigation tasks)? Future recordings of central vestibular nuclei neurons in freely moving mice might bring an answer to this question. Finally, how would a change of gravity affect the neuronal properties of central vestibular neurons? Comparison of these properties in wild-type mice exposed to hypergravity during development and in vestibular-deficient mutant mice will give more insight into the functional role of vestibular sensory signals in the acquisition of proper locomotion and navigation capacities.

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REFERENCES