The neurological mechanisms underlying our sense of balance

We owe our sense of balance to an intricate chain of interactions between organs in the inner ear and the brainstem. Understanding how this system goes wrong is crucial to searching for new cures which could in future help people suffering from vertigo. Dr Soroush Sadeghi's lab at the University at Buffalo is at the forefront of studying these neurological mechanisms and understanding how the system attempts to compensate when it has been damaged by diseases which affect the inner ear.

Balance is an automatic function for most people: we only become aware of it when something goes wrong.

Of all our innate physiological senses which enable us to fluidly carry out our daily lives, our sense of balance is perhaps the one that we are least consciously aware of. It prevents us from falling over when standing or moving and facilitates clear vision during movement, which enables us to read signs during driving or walking.

We owe all of this to the vestibular end organs in the inner ear which interact with neurons in the brainstem. The vestibular organs detect head movement and encode it into electrical signals that are sent to the brainstem and the neural structures that control eye muscles and muscles of the upper and lower limbs as well as higher brain centres that provide information about our posture and spatial orientation.

The Sadeghi lab uses a variety of experimental approaches to investigate mechanisms of efferent-mediated afferent modulation.

This all happens so automatically that we only become aware of it when the vestibular system malfunctions or stops working altogether, as is the case for people who suffer from vertigo which can develop through illness or natural ageing processes. Research suggests that various forms of vestibular dysfunction are present in at least 35% of Americans over the age of 40.

EXCHANGING INFORMATION

Despite the importance of our sense of balance, scientists still know relatively little about the variety of ways through which the vestibular system and the brainstem exchange information.

So far, they have found that these processes are mediated by two important types of nerve cells in a continuously adapting feedback loop. Vestibular afferent neurons (afferents) carry signals from vestibular hair cells in the inner ear to the vestibular nuclei in the brainstem and efferent neurons (efferents), also located in the brainstem, transport feedback to hair cells and the afferents.

There are two populations of hair cells in the inner ear, pear-shaped type I cells and cylindrical type II cells, which form synapses with different types of afferents. Type I hair cells form synapses with calyx-shaped afferent terminals, whereas type II hair cells form smaller bouton-shaped afferent terminals. Both type I and type II hair cells provide inputs to dimorphic afferent fibres.

The afferent nerve fibres have different electrophysiological properties. Calyx afferents fire electrical signals irregularly, bouton afferents have a more regular firing pattern, while dimorphic afferents' firing patterns lie somewhere in between the two extremes. The overall pattern of afferent signalling sent to the brainstem depends on the type of afferents which are activated by the inner ear.

The irregular firing pattern of calyx afferents is thought to be a crucial mechanism which allows the vestibular system to deal with the rapid head movements that occur when running or playing sport, or to compensate when the vestibular system has been damaged through diseases that affect the inner ear such as labyrinthitis or Ménière's disease.

The processes which induce this irregular firing have long remained a mystery.

Dr Soroush Sadeghi, an assistant professor in the Center for Hearing and Deafness at the State University of New York at Buffalo, has been investigating whether the interaction between efferents and afferents could be critical to the vestibular system's ability to adapt when things go wrong.

EXISTING THEORIES

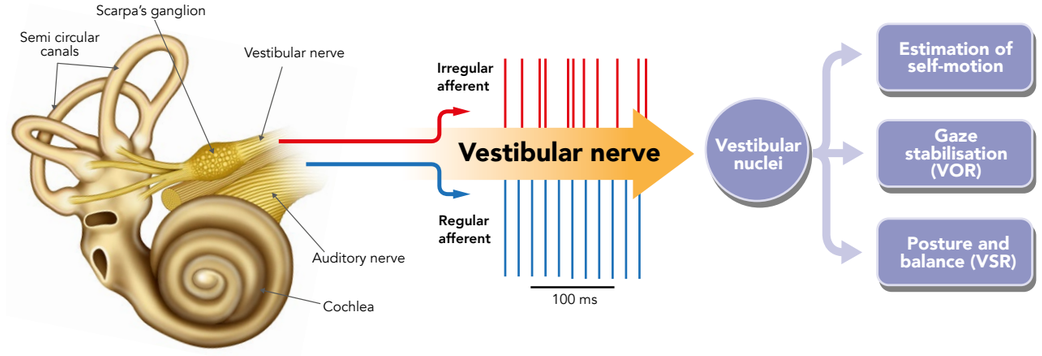
Over the past decade, scientists have hypothesised that certain biological adaptations following illness or natural environmental changes can modify the properties of afferent synapses at their terminals – specialised regions where chemicals called neurotransmitters are exchanged between cells to pass on signalling information.

In addition to changes in chemical synaptic transmission, changes in intrinsic membrane properties of nerve cells through changes in the activity of different ion channels could also alter neural firing patterns. The vestibular system could use such modifications in membrane properties in order to adapt and try to maintain reasonably normal balance when vestibular damage occurs.

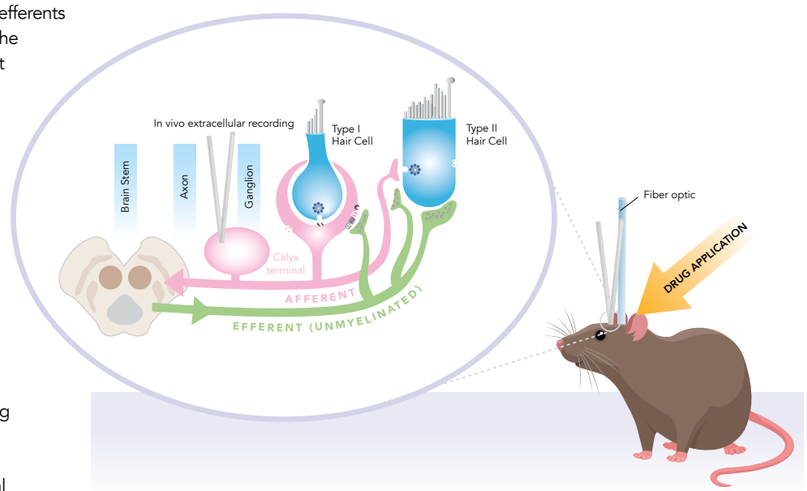
But how exactly does this happen?

Sadeghi believes that one possible way that vestibular compensation could occur is through changes in the activity of ion channels in the afferent neuron cell membrane by chemical neurotransmitters released on them by efferent nerve fibres, which transport information from the vestibular nuclei in the brainstem back to the inner ear. There are two main types of efferent neurons – cholinergic efferents which carry the neurotransmitter acetylcholine, and GABAergic efferents which carry the neurotransmitter ɣ-Amino Butyric Acid (GABA).

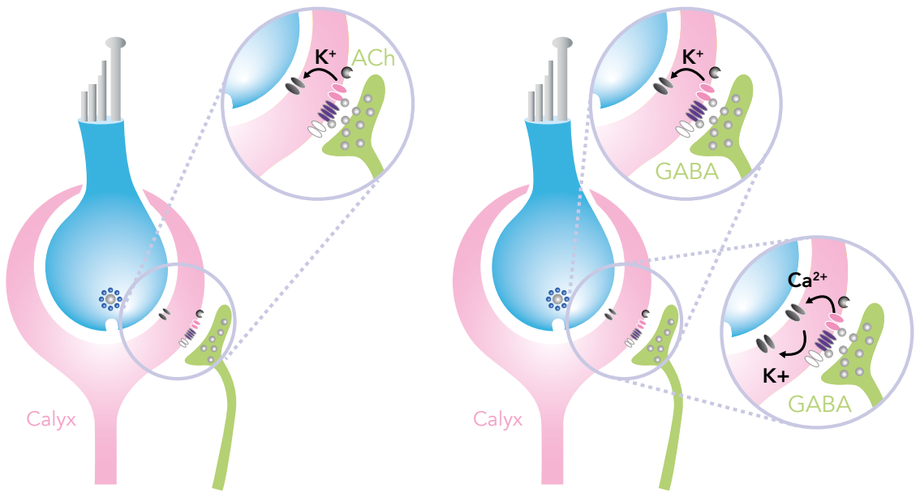
THE MAMMALIAN VESTIBULAR SYSTEM



The peripheral vestibular organs (three semicircular canals and otholits) are located near the organ of hearing (cochlea) in the inner ear. Information about head motion is carried through two afferent channels in the vestibular nerve (regular / tonic and irregular / phasic afferents) to the vestibular nuclei in the brainstem. These signals are then used to stabilise gaze and posture and provide information to higher brain centers.



Vestibular hair cells (type I and II) and afferent terminals (calyx and bouton) are located in vestibular organs. Efferent signals from the brainstem are transmitted to type II hair cells and afferent terminals. To understand the mechanisms of efferent-mediated modulation of afferents, Sadeghi's research group study efferent mediated changes in single vestibular afferent fibers in mice. Different types of efferents are excited or inhibited by optical or thermal stimulation through fibre optics positioned along the vestibular pathway combined with drug applications into the ear.



Efferent inputs could modulate the activity of afferents by changing different ion channels in cell membranes of hair cells and afferents. Cholinergic efferent inputs could inhibit potassium (K^+) channels and increase afferent sensitivities. A second group of afferents that contain GABA could potentially affect potassium channel activity either directly or through a calcium (Ca^{2+}) mediated pathway. The Sadeghi lab studies these cellular mechanisms by using a combination of patch clamp recordings and optical, thermal, and pharmacology manipulations *in vitro*.

Recent studies conducted in a variety of species ranging from macaque monkeys to toadfish have appeared to confirm the neurotransmitter-based nature of vestibular compensation signalling from vestibular brainstem neurons to vestibular afferents. Most notably they have shown that cholinergic efferents exert powerful effects on afferent firing and sensitivity, i.e., the release of acetylcholine from vestibular efferent fibres has a significant effect on the activity of afferent fibres and vestibular hair cells.

NEW STUDIES

The potential consequences of both cholinergic and GABAergic efferent stimulation on afferents are being investigated by Sadeghi's research group.

Sadeghi's lab uses a variety of experimental approaches to investigate changes in afferent firing by these two efferent pathways, as well as the underlying cellular mechanisms by using immunohistochemistry and electrophysiology approaches *in vivo* and *in vitro*.

Previous studies suggest that the activity of neurons in the vestibular nuclei and the vestibular nerve change from tonic (i.e., responding to slow movements) to a more phasic pattern (i.e., responding to fast movements). This functional shift is probably mediated by changes in calyx membrane potassium channels through cholinergic inputs. However, Sadeghi's group believes that this is only part of the story and that GABAergic efferents also play a role in this tonic-to-phasic shift in neural firing through modulating calcium and potassium channels.

Future studies by Sadeghi's lab aim to further elucidate this tonic-to-phasic shift in firing and to also explore the effect of the two efferent pathways on firing properties of afferents in response to rotational movements.

The potential consequences of both cholinergic and GABAergic efferent activation on afferents are being investigated by Sadeghi's research group.

The vestibular system is responsible for the balance that allows us to carry out everyday tasks like walking as well as enjoyable leisure activities.

IMPACT

It is hoped that gaining a better understanding of the functioning of the vestibular system and, in particular, the ability of the system to modulate itself through information feedback transmitted between afferents and efferents, could provide the basis for new drug discovery approaches for patients with vertigo and other symptoms of vestibular dysfunction.

Behind the Research

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Research Objectives

Dr Sadeghi focuses on the neural mechanisms of the vestibular inner ear. In particular, he is interested in vestibular efferent modulation of afferent activity.

Detail

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Bio

Soroush Sadeghi received his MD degree from Shahid Beheshti University (Tehran, Iran) under supervision of Dr Nayer Rassaian. For his PhD, he moved to Canada and studied compensatory changes in the vestibular nerve and nuclei in non-human primates in Dr Kathleen Cullen's lab at McGill University. He then moved to the US and studied synaptic transmission in the vestibular periphery in Dr Elisabeth Glowatzki's lab at Johns Hopkins University. Since 2013, he has been an assistant professor in the Center for Hearing and Deafness (Dept. of Communicative Disorders and Sciences) at the State University Of New York at Buffalo where he studies efferent mediated modulation of vestibular-nerve afferents.

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References

Mathews MA, Camp AJ, Murray AJ: Reviewing the Role of the Efferent Vestibular System in Motor and Vestibular Circuits. *Frontiers in Physiology*. 2017 Aug 2. PMID: 28824449.

Cullen KE, Minor LB, Beraneck M, Sadeghi SG: Neural substrates underlying vestibular compensation: contribution of peripheral versus central processing. *J Vestib Res*. 2009. PMID: 20495234.

Eatock RA, Songer JE: Vestibular hair cells and afferents: two channels for head motion signals. *Annu Rev Neurosci*. 2011. PMID: 21469959.

Sadeghi SG, Minor LB, Cullen KE: Neural correlates of sensory substitution in vestibular pathways following complete vestibular loss. *J Neurosci*. 2012 Oct 17. PMID: 23077054.

Sadeghi SG, Pyott SJ, Yu Z, Glowatzki E: Glutamatergic signaling at the vestibular hair cell calyx synapse. *J Neurosci*. 2014 Oct 29. PMID: 25355208.

Personal Response

In what ways do you hope that understanding the vestibular system in greater detail will help us develop better treatments for vertigo and other vestibular dysfunctions?

"Typically, drugs used for treatment of vestibular disorders are nonspecific and are used for symptomatic relief. These include general suppressants (such as anticholinergics, antihistamines, and benzodiazepines) and anti-emetic drugs. Based on the results of recent studies, we now know that the sensitivity and response properties of hair cells and afferent terminals could be modified and adjusted through efferent feedback. Understanding the specific receptors and channels that underlie such modifications provides the basis for treating patients with drugs that activate or inhibit these receptors and channels with high specificity in patients. Furthermore, application of these drugs directly into the ear provides local effects and further increases the specificity of the treatment."