HHF Research Webinar Transcript
Vestibular Hair Cells: Stabilizing Vision and Balance | April 22, 2024, 5pm ET
Ruth Anne Eatock, Ph.D.

ANIL LALWANI - Well, hello and welcome to our Hearing Health Foundation Research Webinar. I'm Dr. Anil Lalwani and I appreciate you joining us today. This event has a live captioner and is being recorded. You can enable closed captions by clicking the CC button in the toolbar at the bottom of your screen. If you need any other assistance using Zoom, please follow the link to the technical guide shared in the chat.

Today, we are in for a real treat, as we'll be talking about the vestibular or balance hair cells with one of our leading experts in the country, if not the world. These balance cells, these balance hair cells, are responsible for sending signals to the brain about head motion and help us in stabilizing our vision and balance.

And if you lose these hair cells suddenly, they can cause vertigo, shaky vision, and general disorientation. So they're very important in our general well-being and getting around. Professor Ruth Anne Eatock will discuss new developments in our understanding of the vestibular hair cells and their synapses in mammals, birds, and reptiles.

Now, by way of introduction, my name is Dr. Anil Lalwani and I'm a professor and vice chairman for research in the Department of Otolaryngology-Head and Neck Surgery, as well as Associate Dean for Student Research at Columbia University Vagelos College of Physicians and Surgeons in New York.

I'm also a board member at Hearing Health Foundation and the head of the HHF Council of Scientific Trustees, which oversees the Emerging Research Grants program, affectionately known as ERG. Now, ERG is a competitive program that award funds to researchers conducting cutting edge hearing and balance research. These grants supported many leaders in our field to become successful scientists, including our illustrious speaker today.

Dr. Eatock is a professor of neurobiology at the University of Chicago. Her research focuses on how the mammalian vestibular inner ear is organized and specialized to provide information to the brain about different kinds of head motions. She's also a recipient in 1987-1988 of the Emerging Research Grants program that we just talked about and a former member of the Hearing Health Foundation's board of directors.

Now, the ERG program that provides seed money to scientists just starting out in the field, research is only possible through the generosity of supporters like you. If you'd like to support our work on hearing loss, tinnitus and related conditions, and balance disturbance, you can do so today at hhf.org/donate. Now, we'll move on to Dr. Eatock's presentation. Please ask questions to the Q and A box linked at the bottom of the screen and we'll try to answer following the presentation. Dr. Eatock.

RUTH ANNE EATOCK - Thank you, Anil. Can you hear me?

ANIL LALWANI - Yes, we can. Yes, we can.

RUTH ANNE EATOCK - Good. All right. Are you seeing my screen, Anil?

ANIL LALWANI - Yes, we are.

RUTH ANNE EATOCK - Great, thank you. Thanks very much for the nice introduction. I'm here to talk to you today about just certain features of the vestibular sensors in your inner ear. It'll be a short introduction, and I'm assuming many people are not even aware of the vestibular part of their inner ear because it doesn't speak very loudly to us. It does its work under the radar, and that's as it should be.

Your vestibular inner ear is shown here in this lovely drawing. The reason I have a young woman running along the beach is that she is able to do that so fluidly and happily in good measure due to her vestibular inner ear providing information about her head motion as she moves. The inner ear is shown in this lovely drawing from Smith, Curthoys, and Laitman, showing the cochlea, which you may be more familiar with as the sound sensor of your inner ear. It's the more recent edition.

The ancient part of the inner ear is actually the vestibular labyrinth shown behind or posterior to the cochlea, which has multiple sensory epithelia corresponding to different kinds of head motions and being stimulated by these accessory structures, some of which you can see and which give the whole vestibular labyrinth its unique appearance.

If we look now, well, let me just say, as an introduction, that the vestibular inner ear, I think Anil mentioned this, it's performing, it's providing the information to reflexes that control eye, oops, sorry, eye position, head position through neck muscles, and body position through spinal cord reflexes, allowing you to maintain gaze, steady vision, and stabilize your body posture as you're rapidly moving. It's also contributing through cortical projections to perception of head motion and a sense of orientation and heading as you're locomoting.

If we look at that beautiful picture again, we see the membrane of this labyrinth, of the vestibular inner ear shown in green. There are five sensory epithelia. Three of them detect angular or rotational head motions, two detect linear or translational head motions as you move forward and back or sideways but without an angular component.

Of course, most head motions naturally will have both angular and linear components to them. And so the net effect on the vestibular nerve will involve output from many of the organs all at once. The rotational sensors are the semicircular canals. You can see the canals which are at 90 degrees or orthogonal to each other.

We have two vertical canals and one horizontal canal sort of, I'm outlining here. And amazingly, these are in sort of Cartesian coordinates within your head and provide sensitivity to motions, rotational motions in those planes. The sensory receptor cells or hair cells are located in these swellings and face the canals that deliver the rotating fluid to them.

In addition, we have the otolith organs, so called, otolith means ear stone. They have crystals within them which confer upon them sensitivity to linear, translational head motions and also to tilt of the head, which changes the gravity vector relative to the orientation of the epithelium.

And you can't, these sensors, like any linear accelerometer, cannot distinguish gravity from a translational acceleration. So there are two of those. One is the utricle, it's shown here. It's a little orange slab. It's approximately horizontal so it's sensitive to motions in many directions in that plane. And then below it is the saccule which is approximately vertical and census rotation motions more vertically.

I'm mostly going to talk about the otolith organs because those are what we study in our laboratory. But I want to begin with the famous horizontal vestibulo-ocular reflex to illustrate something that happens to you all the time, you use every day, it's extremely fast. In fact, it's the fastest reflex we know of, and it allows you to maintain gaze or steady visual fixation while your head is moving in the horizontal rotational, through horizontal rotation.

For example, if someone is fixating a target ahead of them, and we or that person self moves and with an angular rotation, maybe to see something over on the left but wants to, never mind, wants to keep looking at the visual target, that's achieved through the vestibulo-ocular reflex, which begins in the horizontal semicircular canal because this is a horizontal rotation.

And the signals are produced there by the sensory hair cells sensitive to that acceleration and communicated to the eighth nerve fibers, the vestibular nerve fibers, that project neurons in the brain

through several synapses landing on the muscles that cause the motion of the eyes. And through that motion, you get counter rotation of the eyes just enough and at a good speed to maintain visual fixation.

All of this can take place within just several milliseconds as illustrated by data from the Cullen laboratory. So in this case, they delivered a head velocity impulse lasting tens of milliseconds. So that's the gray trace here. So the head, sorry, the head went through an abrupt motion and they monitored the eye velocity that was produced by that in order to maintain fixation. And the eye velocity was just a few milliseconds delayed relative to the head motion.

This is a five millisecond marker, 0.05 seconds. So that whole event took place involved sensing and motion of the information through multiple neurons and synapses, the points of contact between neurons in the pathway.

Now, there are probably a number of features of this system that facilitate the really rapid transfer of information. The reason is that this is the only system, the evolutionary need for this, is that this is the only system you have that can provide information in time for compensatory eye motions or head and body motions, for that kind of motion, in time to compensate for the motion, allowing you to maintain a steady gaze or body posture as your own head is moving.

Let me just review, or not review, look a little more closely at how signals pass through the system. So here we have the vestibular inner ear, the utricle and saccule, we're highlighting the utricle, which is an otolith organ that detects linear acceleration. And there are two kinds of afferents that emanate from the sensory epithelium. So these afferent nerve fibers, they're part of the vestibular nerve. They make synapsis or contacts with the hair cells in the sensory epithelium.

Those hair cells are sensitive to, in this case, horizontal, linear translations, and carry information about that to the brainstem, the cerebellum, from the brainstem to the motor nuclei, also in the brain, that drive eye muscles to give you the ocular reflexes that I just gave you an example of, or spinal reflexes to maintain body posture.

There are also projections through the cerebellum. One thing, one important feature of that projection is compensation for gravity effects. So within the cerebellum, a model, and there's an internal model that builds up with experience of how gravity is likely to affect linear accelerations that are sensed by the otolith organs.

And then from the brainstem, there are thalamocortical projections which ultimately contribute to your perception of head motions and your sense of orientation or heading. And all of these perceptions, orientations, and reflexes are at risk if you have damage to your inner ears.

Because vision and proprioception, other senses that can provide information about the attitude of your head or your body posture, those operate too slowly to provide useful information to allow online compensation while you're actually moving at frequencies above just one or two hertz.

That's just one head motion per second. Within that time, these other systems can provide useful information, but beyond that, at higher head motion frequencies, you need your vestibular pathways. It's the fastest kind of information available to the brain.

The afferent nerve, I'll just mention, it's shown to have two channels, an irregular channel and a regular channel. By that I mean that there are two kinds of afferents with different kinds of encoding strategies exemplified by the different timing between spikes or action potentials or neural impulses within the nerve fibers.

The irregular pathway timing is very irregular and the regular pathway, it is very regular. And as a result, these two pathways use different strategies, one or more temporal strategy, and the other a rate-based strategy. So having run through the central nervous system at an alarming clip, I will return to the vestibular inner ear and talk more about how it is organized. So here, I'm focusing on another otolith organ. The saccule, the vertical linear acceleration sensor.

Here's a cartoon of the saccule. Like the utricle, it has that central strip called a striola, which gives rise to the irregular afferents. And then around that, the extrastriola gives rise to regular afferents. Now here we look at a cutaway drawing of the saccule. The epithelium is on the bottom. You can see

maybe cartoons of hair cells located within it. And protruding from the apical surface of the epithelium are hair bundles.

These are arrays of specialized cilia that contain within them the mechanosensitive ion channels that respond to motion of the bundles. They connect to an overlying gel layer, which supports a mound of calcareous crystals which are denser than the surrounding fluid.

If you were to move in this direction, say towards the bottom right corner, the relatively dense crystals would lag the motion of the underlying epithelium. And that would cause deflection of the hair bundles, which are connected to the crystals, through the gel layer at their apical tips, and to the sensory epithelium through their cell bodies at their basal ends.

You would naturally get motion of the hair bundles back and forth, back and forth motions of the head producing back and forth lags of these crystals, which are called otoconia, which means ear pebbles. And this is, altogether, forms the otolith, which is why it's called an otolith organ.

You remember that we talked about the irregular afferents coming from the striola. Just wanted to point out the differentiated structures at every level of this striola. The crystals are smaller, the gel layer is more porous, the hair bundles are shorter, more compact and stiffer, and they get more of a fluid communicated stimulus. Whereas in the extrastriola, those are driven more by the displacement of the gel layer.

All of these differences are likely important in the different sensitivities of the irregular afferents relative to the regular afferents. And in fact, these afferents carry more high frequency information. In addition, I'll talk more about a specialization that may also affect and occurs at the level of the hair cells.

Okay, so there are the firing patterns that you get for the striola and the extrastriola again. Okay, so now let's look even closer at the hair cell types that are present within the epithelium. So here, we're looking at a beautiful transmission micrograph. So we're looking at cross-section through the epithelium and we're just looking at several cells. So we have a hair cell, a supporting cell, and another hair cell. So the first hair cell is similar to hair cells that you find in most vertebrate inner ear organs and lateral line organs. It's approximately cylindrical and it's contacted by a compact synaptic terminal from the afferent neuron.

Remember you have afferents synapsing with the hair cells to carry the information to the brain and they form, the afferents form little boutons, which are opposed to the, I'll get to that in a second, sorry, which face presynaptic structures as well in a minute. But on the type one hair cell, the other hair cell type, there's an extended calyx or cup-shaped terminal that engulfs the entire basolateral membrane of the cell, like a glove.

If we look at these cartoons to the right, you see the green, type two hair cell, it's called, the type one hair cell, which is inside the yellow calyx which extends all the way around it. It's not perforated, it's fully intact. So it entirely surrounds the hair cell, the type one hair cell membrane.

And you see the third cell type, the supporting cell right here. Now the supporting cell is special to the sensory epithelium. It's a sister cell of hair cells. And in fact, in these vestibular epithelia, even in mammals, there is some capacity for these cells to transform to hair cells.

So for example, if there's a lot of damage to the vestibular epithelium, to the hair cells, then some of the supporting cells will transform towards the type two hair cell. And while this kind of regeneration, it's called hair cell regeneration, it's not enough to produce obvious functional recovery of the vestibular function.

It's very promising, it forms, there are a lot of experiments being done to try to promote further regeneration of hair cells both in the vestibular epithelia and also maybe to transfer some of that knowledge to the cochlea where no regeneration occurs at all in mature epithelia. So there's a lot of interest in that capacity of the supporting cells to become hair cells.

Now, I'd like to point out the synaptic cleft. It's very different in the two hair cell types. So you have this little small synaptic cleft. The cleft is just the liquid-filled space between the hair cell and the primary afferent. And it's very, it's about 20 nanometers, very small distance. And here I've drawn in the

synaptic structures that are typical of hair cells. They're sort of organized clusters of spheres containing the excitatory transmitter glutamate.

These structures are typical in hair cells. We also see them in type one hair cells and they produce what's called quantal transmission of the receptor potential signal of the hair cell to the postsynaptic terminal. So the receptor potential modulates the release of the transmitter and that produces a response in the postsynaptic terminal, which triggers action potentials. That's called quantal transmission.

In contrast, well, we see the same thing with some type one hair cells under calyxes, but there's a novel form of transmission that may be unique to this particular synapse and facilitated by this large calyx and also by the expression of unusual ion channels in the type one hair cell.

Let me proceed to talk about how we study the signals that drive synaptic transmission. So hair cells, like the afferents and neurons in the brain, all use electrical signals which are generated by the flow of ions through proteins that open up to form channels in the cell membrane. So when you move the hair bundle of a hair cell, here we're looking from the side at a calyx forming, an afferent forming a complex calyx around several hair cells, which can sometimes happen.

You have several type one hair cells and we're moving the hair bundle of one of the hair cells and we can record with probes from the hair cell or from the calyx. This is all possible because we can study these sensory epithelia. We can take them out and look at them under a microscope and bring probes in under visual control. So with that ability, we can look with a bird's eye view on the epithelium and see the hair bundles of the hair cells and bring in a probe to move the bundle.

Note that we've taken the overlying accessory structures away. So we're going to directly move the bundle with probes and then rerecord from the hair cell with an electrode, making contact directly with the hair cell and actually breaking, punching a hole into it that allows it to fill the hair cell with the fluorescent dye.

Or we can record from the calyx afferent and we can fill that with fluorescent dye. And this shows you an example of a triplet like this where there are three type one hair cells. They don't get filled by dye. They're outlined by the dye-filled calyx because there's no direct connection that's large enough for the dye to flow through from the calyx into the hair cell.

This novel form of transmission that we now know exists at these synapses does not involve direct flow of large molecules from one cell to the next. So just to mention some of the ion channels involved in making these electrical signals, there are the transduction channels at the tips of the stereocilia, which open and close depending on the position or deflection of the hair bundle. So deflection in one direction sort of pulls in those channels, pulls them open.

And when they're open, ions enter in vivo. The ions are principally potassium ions. So those are positive ions that enter, and that entry of positive charges into the cell changes the membrane potential and that activates a bunch of ion channels in the cell membrane, notably potassium selective channels.

These are different kinds of channels, but they all pass potassium, and those are the dominant ion channels in hair cells. And then together, these channels work together to create a receptor potential, which is the voltage change caused by the entry and transmembrane movement of all of these ions. And that triggers transmission onto the afferent where sodium and potassium channels generate spikes or action potentials.

Let me just show you some of the signals that we can see. Here, we're using a probe to move the hair bundle and we're driving it with a protocol, which is a series of sinusoidal deflections at different frequencies from two hertz, which is, you know, two cycles per second to 5, 10, 20, and up to 100 hertz.

So this covers most of the physiological range of vestibular hair cells. In particular, head motion frequencies are most prominent below 20 hertz, although there may be some at higher frequencies. And above, you see the transduction current that flows through the channels of the hair bundle as the hair bundle is moved back and forth by these deflections.

Okay, so we're moving the hair bundle back and forth with the sinusoidal wave form and recording the signals that it makes. And you can see it makes an oscillatory signals the stimulus that's being applied. So let's look at how that signal is changed as we move through the hair cell and afferent. We have the hair bundle deflection again, and then the transduction current again. But now we also see the voltage change that the transduction current makes.

As positive ions enter, they're going to change the transmembrane voltage. And you can see that here. And now, we're seeing that, again, oscillatory receptor potentials, there's quite a large increase in gain of the response. This is a much bigger signal than the current was, but there's also more shaping of the response so that the response gets smaller at high frequencies. Then we jump the synapse.

And now this is an immature calyx, and we're just looking at quantal transmission, that is this receptor potential is producing release of glutamate onto the postsynaptic membrane activating channels that bind the glutamate and producing these really interesting looking oscillations that are quite different from what the hair cell has. They have a sort of skewed shape.

Here are the postsynaptic potentials. Here are the postsynaptic currents that give rise to the potentials. When the potentials are large enough, they trigger spikes. So see, this is just two millivolts, this is 25 millivolts, and these are very much larger. The spikes are the all-or-none action potentials that are generated in the nerve fiber at a little distance from the postsynaptic membrane. They're important because they're the signal that goes to the brain. The spikes are large and they can regenerate along the nerve fiber and carry the signal to the brain. These small signals would die out too soon without spikes.

Okay, so we've gone from presynaptic hair cell responses to postsynaptic calyx and afferent responses in an immature synapse, just a developing, still developing inner ear. Once again, an immature calyx recording. As the synapses become more mature, as the inner ear gets more mature, we start to see a really unusual form of transmission that hasn't been described at other synapses.

And that is a quite fast form of transmission that doesn't seem to involve glutamate or release of packets of glutamate. And so it's called non-quantal transmission because the quanta refer to the packets of glutamate and this seems like a more smooth process, a more smooth delivery of the signal across the synapse. Here, we've truncated the top of the response because those are spikes. So these are big enough responses to generate spikes, one for each oscillatory non-quantal response to the hair bundle motion.

Just looking at these, you can see that they look different in a number of ways. There's more information about both cycles of this, both the positive-going and negative-going half cycles of the stimulus. So it's a more linear response. It's also significantly faster, as I'll get to in a minute. And then sometimes we see evidence for both together. But I have to say, mostly we're seeing mostly non-quantal transmission, which may reflect the greater sensitivity of quantal transmission to the conditions in our somewhat unphysiological preparation where the epithelium is outside of the animal.

Right, so quickly to wrap up, how might this strange transmission be operating? Well, we intuited that it might involve both the calyx and specialized channels that are only present in the type one cells and the postsynaptic membranes that mean that there are a lot of open channels at the resting potential. These are called GKL for low voltage activated potassium conductance channels. There will not be a test of that. These channels are present at very high density in the hair cell and then they have corresponding channels that happen to be different in the postsynaptic membrane.

But we wondered if during a hair bundle deflection, the potassium would enter those mechanosensitive channels, which are off the top of the screen and flow through open channels in the membrane and directly transmit to the postsynaptic calyx by the direct flow of ions from one cell to the next through these open channels across the very small distance of the synaptic cleft.

This was a fun idea to think about. We wanted to have, oh, let me just say we do know something about the channels. You probably don't need to know their molecular identities. They're different on both sides of the cleft. But the immuno-side of chemistry shows that there just are a very large

number of those channels, both in the hair cell, the magenta here, and in the postsynaptic membrane in the calyx. And they're different. They're not just different colors, they're actually different proteins.,

In order to make this intuition about how the non-quantal transmission more sturdy, we recruited our colleagues Rob Raphael, Imran Quraishi, and most recently and prominently, Aravind Govindaraju, to work with Anna Lysakowski and me to build a realistic model of the type one hair cell calyx synapse.

Anna and I provided data about actual synapses and Aravind and his colleagues built a model as realistic as they could make it given the information that's available, which is quite extensive, and it includes the geometry of the calyx and the hair cell and also all of the ion channels that are present in both the hair cell, in blue, and in the calyx. And this model is very successful at capturing the important properties of the non-quantal responses that have been recorded in vivo by our lab and also by Donatella Contini and Jon Art.

And the model shows, or works, obtains those results through two kinds of non-quantal transmission, one is a sort of slow component due to the rise in potassium within the synaptic cleft, which takes a while after the start of a stimulus. So here's a hair bundle deflection and here's a larger one.

As you start the stimulus, the potassium slowly increases in the cleft and that is a direct excitatory effect on the postsynaptic membrane, which is what we're recording here. In addition, there's a little fast component, a sort of electrical, direct electrical effect that is much faster, and that produces the very short latency nature of this non-quantal transmission.

Put them together, so here's the electrical effect, put them together and you get the red trace and you can see that together you get a spike and with each one by itself, no spike. So working together they can make the transmission more sensitive.

I'll conclude just by stating that type one hair cells only occur in amniotes. They have specialized properties that create an especially fast and effective form of transmission that is called non-quantal transmission. And why is that true? Why is that true only for hair cells in the vestibular epithelia of amniotes?

Well, one can only speculate about evolution but amniotes arose when animals moved from living in water on to land and into a really less supportive kind of environment, right? So with the transition to land, locomotion is entirely different. You go from being supported by water as a colleague of mine once said. It's hard to fall in water where it's very easy to trip on land or to plummet from the sky.

And so with these more challenging environments, there might have been a need for really super fast transmission and reflexes to allow you, and accurate reflexes, to better support compensatory motions as you move across the terrain, the challenging terrain of the planet.

So with that speculation, let me thank the colleagues some of whose work I've shown, some of the colleagues whose work I've shown and funding sources including Hearing Health Foundation, which gave me my, as Anil said, I think gave me my very first funding. Thanks.

ANIL LALWANI - Dr. Eatock, that was terrific. We have several questions. We thought we might start with something very broad and general. So Richard asked, we have two vestibular inner ear structures. Do they function jointly or independently?

RUTH ANNE EATOCK - So Richard may be talking about, there are several dichotomies, there are a lot of dichotomies in what I said, possibly in a not very coherent way. If you mean angular accelerometers versus linear accelerometers, I think most head motions will simultaneously engage several, if not all, of the vestibular epithelia that you have on each side of the head. Maybe you were talking about both sides of the head. Those are always going to be engaged in sort of a complimentary fashion. And the brain makes good use of having two and having information in one direction on one side and the other direction on the other.

But there are also those two channels of afferents which there's very lovely work, maybe particularly from the Cullen Lab showing that having those different firing patterns, irregular and regular, allow decoding of different kinds of information with different kinds of sensitivity. So it's really doubling the information available from a given head motion to have those different properties. I don't know if that works. And then otolith, then canals, it's angular and rotational and linear, and you just need to know about both.

ANIL LALWANI - So there was a, this is an interesting question about recovery, but Claire said she lost her hearing but also had severe vertigo four years ago. And basically now, she feels like she's almost back to normal. Can you talk a little bit about compensation that occurs after loss of unilateral vestibular input or anything? Or how do we deal with it? Is it a brain thing? Is it a year thing?

RUTH ANNE EATOCK - Yeah, so there is a whole field of research devoted to understanding compensation. And usually, what scientists mean when they're talking about that is sort of plasticity. The vestibular system is remarkably plastic even as we get old. So it has to, synapses within that system have to adjust gain. So if you're trying to have the perfect eye motion for a given head motion, you need to have the right gain. And that depends on the focus length to your target. And that's going to depend on whether you're wearing your glasses or not.

So you have this sort of daily difference in gain. At least many people I know have glasses, but there are many other... The gain depends on how far away something is, what you need to have. And so it's constantly being updated. And after loss on one side, so there are a number of conditions where you get struck on one side but not the other, the brain can do quite an effective job of recovering from that damage. Now, I don't know if Claire had the misfortune to have sudden loss on both sides.

ANIL LALWANI - Just one side.

RUTH ANNE EATOCK - Just one side, I didn't hear that, okay. And we don't need to talk about that. The other situation, compensation of that sort can't really happen if there's total loss of the vestibular inner ear. And then I think what people are talking about when there's total loss of vestibular information is that people make really remarkable adjustments. For example, they don't move their head very much because it's so disorienting, because they can't compensate for it.

ANIL LALWANI - Yeah, I remember reading somewhere that one of the things that separates rodents from us or us from rodents is that the rodents will continue to circle if they have a injury, whereas we actually learn to compensate and not always circle, you know, for days on end.

RUTH ANNE EATOCK - Yeah, I guess I don't really blame the rodents. I just think theirs is built a little differently than ours and we just lacked that circuit. But I think the general thought there, or one of the thoughts is that it's not so much related to spinning because of aberrant, you know, acceleration input, but rather that there's a loss of, the vestibular nerve carries a tremendous volley of information into the brain. And so you have a sort of denervated, denervation of parts of the brain and it's sort of like a, it's almost like a tinnitus related to the vestibular loss. Anyhow, I'm glad that Claire was able to compensate so well.

ANIL LALWANI - Yeah, so you know what? Your diagram showed a wonderful, the peripheral ear, the vestibular ear, all the way to the brain and all the different interactions occur. Can you talk a little bit about aging of the balance system, both peripheral, central? You know, why do we get dizzy when we get older? Or any of those questions would be great.

RUTH ANNE EATOCK - Okay. So my understanding is that like all the senses, things sort of trick along. We're sort of at peak performance as young children and then we're quite good. And then about late middle age, like 60, things, the numbers of hair cells fall, and I'm not sure if we know about that capacity to regenerate, but so far it hasn't been an issue because it's limited enough that we don't have evidence that we can by regeneration recover function, even in a young animal, in a young experimental model.

You lose a lot of vestibular function. As usual, you don't really know about it because you don't have anything you consciously attribute to your inner ear, but you just know that your balance isn't as good. Maybe your gait gets wider. So what you see, so senior people who I think have lost a lot of their vestibular inner ear, they often have a wider gait just to give them more balance, sort of like sailors on a ship, right? So we make a lot of behavioral adjustments.

And then in terms of what you can do, there are some nice new efforts to be more aggressive in therapy. So galvanic vestibular stimulation is being tried in a number of different ways by an effort, not just within clinical experimental settings, but also by some companies that are getting started. And that has an intriguing potential to help people compensate. I don't want to get into the details, but I think there's a lot of interest now and a lot of people are seriously taking the idea that we could do more with rehabilitation and practice and also some electrical therapies.

Finally, there's clinical trials on vestibular implants, which are like cochlear implants. And those are interesting and promising. The challenges are different, but I'm hopeful that those will be able to restore function. And in that kind of case, you just have sensors of the head motions, just like your inner ear provides. You bypass the inner ear and you provide signals related to what those sensors are picking up directly and electrically to the vestibular nerve.

ANIL LALWANI - You actually anticipated a question that was asked about the vestibular implant, so that was terrific. Now, you commented that regenerated hair cells and the balance system don't necessarily function. Did I hear that correctly? So there's no hope for hair cell regeneration and the--

RUTH ANNE EATOCK - No, there's hope. There's hope. But so far. So the backstory, and I must say I'm a collaborator with a key figure in this, this area for vestibular epithelia, Jenny Stone and Brandon Cox and others who've worked with those two. So we've done a little work and to assess the function of the individual hair cells and the regenerated hair cells, the naturally regenerated hair cells that come back after a lesion, they're not stimulated by, you know, genetic, transgenics or anything. They just come back through that response I mentioned by transformation of support cells into hair cells.

So you see hair cells, you get maybe 20% of the hair cells recovering. But what you don't see is that the experimental models, who happen to be mice, they don't stop spinning, they don't restore their posture, they can't walk across the balance beam. They just don't recover functionally. That's what I mean about the function. But if I record from, or more properly Tony Gonzalez Garrido recorded from the hair cells, they have transduction currents and those voltage potassium currents. And you can see Jenny and her colleagues have shown recovery of synapses that look functional.

But what seems to be the case is that there isn't an adequate stimulus. So either you just need 80% rather than 20%. The other thing is I did talk about how the support cells would become type two cells, but they never, the type two cells never become, there are no type one cells. And so maybe that's another indication of how important type one cells are to the total vestibular function.

ANIL LALWANI - That is so interesting. Bill Brownell. Hey, Bill. He has a question for you.

RUTH ANNE EATOCK - Hi, Bill.

ANIL LALWANI - Do you think loss of NQT by damage to the calyx could cause problems with the fast vestibular reflexes?

RUTH ANNE EATOCK - Yes.

ANIL LALWANI - Well, Bill, there you have it.

RUTH ANNE EATOCK - I mean, so I think there's evidence, sort of a history of evidence that synaptic transmission is vulnerable in the vestibular inner ear as it is in the cochlea. It's long been known now that a lot of hearing loss is perhaps more attributable to synaptic damage between the hair cell and the first synaptic contact from the afferent. Same in the vestibular epithelia, and particularly sensitive appear to be the type one cells and the synaptic calyxes.

It's, you know, maybe, sort of homeostasis. These are really high flying synapses. These are the fastest, this is the fastest synaptic transmission that's been measured. It's faster than cochlear transmission. People who work on hearing organs get very annoyed at me about that but--

ANIL LALWANI - I know, I too am kind of jealous that it is that way.

RUTH ANNE EATOCK - Very impressive, and when things are working that hard, then they're sensitive to aging kinds of, you know, just wearing out and accumulated damage.

ANIL LALWANI - So there's a follow-up, very specific question from Ahmed Eladly. What would be possible explanation for why these hair cells have a resting discharge other than to have a way to encode directionality?

RUTH ANNE EATOCK - Well, I like encoding directionality, but I mean, different sensors can work differently, but if you poise the system so that there's some resting discharge, even if you're only conveying information in one direction, the slope of the function is steeper if it's partly turned on. Do you know what I mean? So if you make small motions around arresting discharge, you'll get a more linear response and a faster response.

And on average, they're just advantages to being partly turned on. But I think for the vestibular inner ear, the sensitivity in both directions, which I didn't really focus on but the questioner knows, is an important sensory function to be able to signal in both directions. I think maybe it's time.

ANIL LALWANI - It's almost getting time. Yes, we're coming down to the last question. We have two for you. One is maybe answer to why people spin in Ménière's disease, but the second one, and you're welcome to allocate your time the way you want to over the next few minutes, what's the future direction, whether it's an understanding of our balance system or whether it's our healing of the balance system or implants, any kind of parting words of wisdom that you'd like to share with us?

RUTH ANNE EATOCK - So because I'm not an expert on Ménière's, which is a really important and difficult problem, maybe I'll just go to future directions. I don't want to, I'll just end up floundering on the Ménière's question. Maybe Anil could take that.

But let me just say for future directions, I'm really excited. I do feel we're kind of at the tip of the exponential, the ankle of the exponential rise in research and in clinical efforts. There's a lot of, I have a lot of hope for the vestibular implants and for these other kinds of therapy that are coming online.

And also just for the general communication between scientists and clinicians these days, I think there are some really good back and forth. A lot of the research is very clinically oriented and performable, I think. I think with time, you know, a few. When I started working in this field, there was very much less attention paid to vestibular. I think there were a lot of occasions, and maybe Anil, you can correct me, but where dizziness was never attributed or often not attributed to the inner ear or the inner ear wasn't considered. It was assumed that it was all in the brain.

And so I think just recognizing and diagnosing the problem is going to be essential for making progress. But I think people are going to be doing that and there are already people trying to work with innovative wearable devices that provide stimulation through the skull to the inner ear, and that that is producing effects in trials as are the vestibular implants.

I'm excited about everybody working together, everybody everywhere, all at once, working together on the vestibular inner ear and joining forces with people working on the cochlea and on hearing, because it all emanates from the same structures.

ANIL LALWANI - You know, I was going to say the same thing. I'm equally excited about the hearing part because they're so similar, you know, and so this is very exciting time for both auditory and the vestibular field, both in basic sciences, as well as its impact on clinical practice. So it's very exciting and your work is very exciting, Ruth Anne.

And I want to take this minute to, you know, thank, I want to thank all the attendees and especially your presentation, Ruth Anne. It was just terrific. We're also all grateful to you, our community, for your support of our Emerging Research Grants program.

Now remember that you can donate to our efforts to advance better treatments and cures for hearing and balance disorders at hhf.org/donate. Again, thank you and please enjoy the rest of your day.

RUTH ANNE EATOCK - Thanks, Anil.