Most readers here are probably familiar with the idea that Endolymphatic Hydrops (swelling of the fluid-filled membranous tube/labyrinth within the ear) is a hallmark of Ménière's Disease. Whilst hydrops probably doesn't cause all the symptoms of Meniere’s, it is likely to underlie most of them, including the severe vertigo attacks. Experts often suggest that Ménière's is probably a “multifactorial disease” because any number of pathologies can alter the inner ear’s ability to regulate the inner ear fluids, leading to hydrops. Why does swelling of the fluid-filled tubes in our ears produce the symptoms of Ménière's? - because the hair cells that sense sound and movement are housed in this membranous labyrinth tube and are extremely sensitive to small fluid pressures, which can occur with just a 20µl volume change (the size of a speck of dust)!

So the real question is - how does the inner ear regulate endolymph volume?

Before we look at the ear, let’s quickly examine how some other parts of the body regulate their volumes, and what happens when this goes wrong. The lymphatic system is a series of ducts that course throughout the body, and is responsible for regulating the fluids in our arms and legs. These ducts have holes or gaps in them, and valves to prevent backflow, so that fluid passively flows into the lymphatic ducts towards lymph nodes, where it is then filtered back to into the bloodstream. Blockage of these ducts, say from bacterial infection or trauma, can lead to an unsightly lymphedema. In the cardiovascular system we have special sensors called baroreceptors that sense an increase in blood volume, which then regulates the release of an ‘antidiuretic hormone’, which ultimately affects the amount of water re-absorbed in the kidney, or expelled in urine. Disoders of baroreceptors, antidiuretic hormone, or kidney function can lead to hypo- or hypernatremia, Diabetes insipidus, cardiac arrest, and abnormal blood pressure, among other symptoms. The kidney also regulates its water absorption via changes in the salt permeability of the kidney tubules (reduced salt permeability leads to increased water excretion). In more sensitive fluid-filled structures such as the eyeball, watery fluid is secreted in front of the pupil, and then drains back through a meshwork at the edges of the iris. Certain molecules in the meshwork sense an increase in eye volume or corneal stretch, and increase the drainage outflow. Additionally, the salt content of the watery solution excreted in front of the pupil is regulated, to alter the amount of fluid produced. Blockage of the iris drainage or abnormal salt regulation in the eye can lead to open-angle glaucoma and blindness.
In each of these systems the normal volume can fluctuate over a relatively large range. That isn’t the case in the ear, which is extraordinarily sensitive to increases in fluid volume – that’s how we sense sound! So how does the ear regulate its internal volumes?

Despite the fluids of the ear being called perilymph and endolymph, the ear is NOT like the lymphatic system. There are no gaps in the compartments of the inner ear, and fluid doesn’t passively flow into or out-of the membranous labyrinth. Rather, water enters slowly through regulated water-conducting protein pores called “aquaporins” in the cells that line the compartment, and essentially only flows into compartments that have a relatively high salt content. Volume regulation in the inner ear is therefore principally dependant on the number of these aquaporins, and the amount of salt transport between the compartments. That said there are also some specialized one-way valves within the inner ear compartments (Figure 2) that can potentially help direct fluid movement towards a kind of lymph-node called the “Endolymphatic Sac”, which can re-absorb some of the fluids (Figure 1). Blockage of these valves or the Endolymphatic Sac due to any number of pathologies or experimental intervention leads to hydrops, causing hearing loss and in some cases, balance dysfunction. Indeed, a great deal of Ménierè’s research has focused on the Endolymphatic Sac. One possible way the Endolymphatic Sac can regulate endolymph re-absorption is through changes in its salt permeability and content. Salt permeability is intrinsically linked to the absorption and secretion of bodily fluids, and there are mechanically sensitive epithelial Sodium channels (ENaC channels), and hormonally driven Chloride channels (Pendrin) in the Endolymphatic Sac, which researchers now believe interact to regulate fluid absorption when volume increases (Kim et al., 2013; Choi et al., 2014). Interestingly, people born with genetic mutations of Pendrin develop hearing loss and endolymphatic hydrops, and it’s believed to be involved in the pathophysiology of some cases of Ménierè’s. Recent research has focused heavily on the role of these types of salt transport mechanisms in the Endolymphatic Sac, and therapies have even started to be developed that may someday help those with such genetic mutations.

Other than regulating fluid outflow via the Endolymphatic Sac, the inner ear can also regulate the influx of endolymph in the cochlea and vestibular system by 1) regulating the salt content of the fluids in these parts of the ear, 2) regulating the number of water pores in the ear, and 3) regulating the ease at which fluid can flow into endolymph through the surrounding tissues. The regulation of the fluids salt content occurs via changes in the number of salt-pores on the walls of the membranous labyrinth or their ability to transport salts, and is key to our understanding of
Ménière’s. Unfortunately, there are many types of salt pores in our ears and the details of how these channels work in concert is complex. In addition to the ENaC and Pendrin channels mentioned above, which are also found throughout the ear, other channels likely to be key players in the regulation of Endolymph volume are the energy dependent Sodium-Potassium transporter (Na\(^{+}\)-K\(^{-}\)-ATPase) channel, a variety of asymmetrical Potassium channels (Kir 2.1, 4.1, 5.1), Chloride uptake channels (Clck-1), Chloride-Potassium transporters (KCC3), chemically driven channels (P2X and P2Y), a Sodium-Chloride-Potassium co-transporter channel, and lastly channels which transport salts directly between cells (gap-junction channels). One only needs to see a schematic picture from an endolymph regulation physiology paper to appreciate the complexity of this system.

However, salt transport is only half the story in regards to water transport. Histology has shown that there are numerous aquaporin channels throughout the inner ear, and recent studies have investigated the effects of changing the number of these channels present in experimental animal ears via treatment with antidiuretic hormones. Such treatment produces mild endolymphatic hydrops with a moderate hearing loss, and in some animals, episodes of vertigo (Egami et al., 2013). Unfortunately, these kinds of results have been difficult to replicate in other laboratories, and the jury is still out on the issue of aquaporin dysregulation as the underlying cause of some cases of Ménière’s Disease.

Allowing more or less water into the endolymphatic compartment via aquaporins is not the only way to regulate the water influx. In order for water to reach endolymphatic compartment, it has to exit the blood and traverse the dense layer of cells that surrounds and supports the membranous labyrinth. Recent studies have demonstrated that an immune challenge to the inner ear can permit more water to exit the blood into the inner ear (Hirose et al., 2014). Additionally, there are certain proteins, such as “Claudin” and “Cochlin”, which are relatively unique to the inner ear tissues and may regulate the ability of fluid to traverse around these tissues, although their precise role is still unclear. In human genetic disorders of these proteins, hearing and vestibular dysfunction develop early or late in life respectively. Cochlin is particularly interesting with regards to Ménière’s Disease and endolymphatic hydrops, due in part to its proposed ability to sense and regulate the volume of extracellular compartments like the aqueous humour of the eye. Whilst Ménière’s sufferers do not have a mutation of Cochlin, its expression can increase during an immune system’s response to infections in remote locations such as the lung, potentially resulting in temporary increases in the expression of Cochlin within the inner ear. Where a person’s immune system incorrectly targets Cochlin, Autoimmune Inner Ear Disorders and Ménière’s Disease may result (Pathak et al., 2013).

The mechanisms leading to abnormal endolymph volume regulation in each Ménière’s sufferer are likely to differ, and therefore so should the treatment, if indeed there is a treatment for the underlying pathology at all. Diagnosing the underlying disorder is unlikely to be as simple as taking a blood-test, clinical measurements of hearing and balance function, or even an MRI. Whilst there are some treatments such as corticosteroid injections behind the eardrum which seem to provide a relatively high-success rate of symptom suppression (or even cessation), no one treatment aimed at resolving the underlying pathology is going to provide the cure-all for Ménière’s. This makes testing the efficacy of new therapies particularly daunting, because a treatment that only provides a mild success rate in a placebo-controlled clinical trial is unlikely to pique the interests of the otology field. The research field therefore has two options, develop more sensitive/specific/simple diagnostic tests, or, develop treatments that only cope with physiological damage caused the entire gamut of Ménière’s Disease by addressing the generation of endolymphatic hydrops.
References


