History of Research in the Vestibular System: A 400-Year-Old Story

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Abstract

Vestibular history starts with the first detailed description of the bony labyrinth published by Casserii in 1610. A more detailed description of the inner ear organs was published by Scarpa in 1789. With refinements in microscopy, descriptions of the microscopic anatomy and the inner ear innervation were published in the late 1800s. Fine structure of the sensory epithelium was described by Wersäll in 1952 using the electron microscope. A functional understanding of the vestibular system has occurred in modern times through studies on the afferent and efferent vestibular system by Goldberg, Fernandez, and Lysakowski. This paper provides a historical perspective on research in the vestibular system between 1610 and the present day.

Keywords: Scarpa; Inner ear; Morphology; Labyrinth; Anatomy; Vesalius

Introduction

Over one-third of adults over the age of 40 have been affected by vestibular disorders finding new an approach to medical care is essential [1]. Multiple advances in the field of vestibular research have occurred steadily since its original description of the labyrinth in 1610, each taking a key step towards the elimination of vestibular disorders. This paper provides a historical perspective on research of the vestibular system from 1610 and the present day.

Overview of the Vestibular System

The vestibular system is composed of five distinct sensory organs that can each be further divided into two distinct regions. The saccular and utricular maculae can be divided into a centrally-located region, known as the striola, and an outer region known as the extrastriola. A similar division can be made in the three cristae ampullares, where they are called the central zone and peripheral zone. Three classes of morphologically and physiologically distinct vestibular afferents, including calyx afferents, dimorphic afferents, and bouton afferents, preferentially innervate these sensory regions.

Anatomy of the Vestibular System

The first detailed descriptions of the vestibular labyrinth were published in "De Auris Auditus Organi Structura" (1610), "Traite de L'Organe de L'Ouie" (1683) and "De Aure Humana Tractatus" (1704) [2-4]. The work of Du Verney is particularly notable for his basic descriptions of the vascular supply to the membranous and bony labyrinth and of various maladies that afflict the inner ear; in addition, Du Verney may be the first to draw the vestibular ganglion as a swelling of cranial nerve VIII, though no mention of this is given in the text [2,5,6]. It is interesting to note that Du Verney surmised that the vestibular system played an auditory role by arguing that since fish do not have a cochlea but can hear, the semicircular canals must respond to sound, possibly by the ampullae acting as "trumpets" amplifying the sound traveling through the semicircular canals.

Prior to the work of Antonio Scarpa in "Anatomicae Disquisitiones de Auditu et Olfactu" published in 1789, much of the work centered on general descriptions of the bony labyrinth and in relation to the cochlea of the auditory system.[8-11]Scarpa described the inner ear of the teleost and humans, drawing the bony and membranous labyrinth from a variety of views and even creating an inner ear model [7-12]. He described the gross anatomy of the membranous labyrinth in detail, including the connections between the semicircular canals and the ampulla. His account of the otolith organs as two stone sacs is the first notable description of the vestibular organs.

It was not until the improvement of the microscope in the late 1800s that Retzius was able to precisely describe the histology of dozens of fishes, amphibians, reptiles, birds, and mammals [13,14]. Careful dissections and silver-stained sections throughout the vestibular system allowed Retzius to see details of hair cells and afferent terminals. Many of his drawings accurately reflect the morphology of vestibular sensory organs and their relationship to each other via the membranous labyrinth; even a cursory examination of his work is sufficient to tell the difference between type I and type II hair cells. Retzius is best known for describing the connections of the auditory and vestibular nerves to hair cells. He demonstrated that the myelin sheath surrounding nerve fibers stops at the basement membrane and does not penetrate into the sensory epithelium, that nerve fibers branch just above the basement membrane before contacting hair cells, that nerve fibers appear to contact type II hair cells at or below the nucleus, that nerve fibers may terminate as cup-shaped endings (now known as calyx terminals) or as small button-like endings (bouton terminals), that a finer innervation morphologically similar to efferent fibers is present in the vestibular sensory epithelium, and that all of these fibers are distinct from the hair cells they innervate (Figure 1) [13-15].

This latter finding is particularly notable since the neuronal doctrine had just been formed a few years prior when it was believed that neurons were individual entities that communicate with each other using synapses [16,17]. The neuronal doctrine was in contrast to
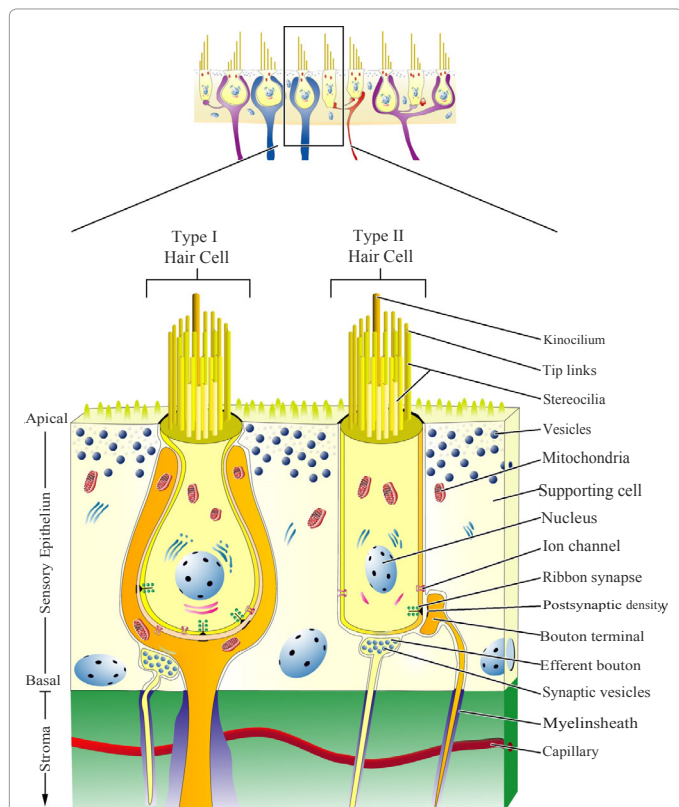
Figure 1: A schematic showing various facets of type I and type II hair cells, their relative locations in the sensory epithelium, and the afferent terminals that contact them. Type I hair cells are surrounded by a calyx terminal (orange), whereas type II hair cells are contacted by bouton terminals. Efferent boutons contact calyx terminals and type II hair cells. These fibers are myelinated once they leave the sensory epithelium. Ribbon synapses are shown in proximity to ion channels and opposite postsynaptic densities located in the afferent terminal. Supporting cells have their nuclei located in the basal region of the epithelium and interdigitate with the sensory cells and calyx terminals. They form tight junctions at the apex with type I and type II hair cells, thereby separating the endolymphatic compartment that bathes the stereocilia and kinocilium from the perilymph that bathes the sensory epithelium. Dark vesicles shown in supporting cells are globules that may contain calcium and help form the cupular and otolithic membranes. The stereocilia are connected to the kinocilium via tip links.

Gerlach's idea in 1848 that the nervous system consisted of a widespread network of filaments in continuity with one another – the reticular theory [18,19]. The hypothesis that vestibular fibers physically contact hair cells originally stemmed from staining artifact through use of the Ehrlich staining method developed in 1882, and was later perpetuated by Kolmer's use of the Cajal staining method in 1904 [20-24]. The debate was not decided in Retzius' favor until the work of Lorente de Nó in 1926), who believed that the results found by Kolmer had "absolutely no basis" and "that in his hands Cajal's method did not give him good results" [25,26]. Other contributions in this era focused on precise basic descriptions of the vestibule and were limited to a general study of the labyrinth and its sensory organs [27].

About a decade after Retzius' first detailed study in the 1890s, Niemack and Kaiser [22,28] made the first detailed sketches of calyx terminals using osmic acid fixation. In contrast to Retzius, they showed these terminals to be composed of numerous, dense granules (Figure 1). It was not until the superior preparation techniques used by Cajal in 1904 that this debate was settled in Retzius' favor [21,29]. Cajal confirmed the findings by Retziusthat calyx terminals and

bouton terminals were the only two endings vestibular afferents use to innervate hair cells (Figure 1) [30]. Shortly thereafter, Cajal described a regional distribution of thick, medium, and thin nerve fibers in the cristae of birds where the thicker fibers were located in central regions and the majority of medium fibers and all of the thin fibers were found in the peripheral parts [31]. Cajal was not as explicit in his findings from macular organs of the trout, which is probably due to the more primitive state of the vestibular system found in fish [32].

In the early 20th century much of the work centered on the patterns of innervation of the inner ear. The vestibular ganglion, its branches to the inner ear, and the morphological characteristics of the nerves were described in the works by Alexander, Wittmaack, Cajal, Lorente de Nó, and Poljak [25,31-35]. These investigations relied on advances in silver staining techniques and better fixation procedures developed in 1936 [36]. In a notable work by Gray, the vestibular labyrinths of dozens of reptiles, birds, and mammals were systematically dissected and photographed (Figure 2) [37]. These species included the whale,
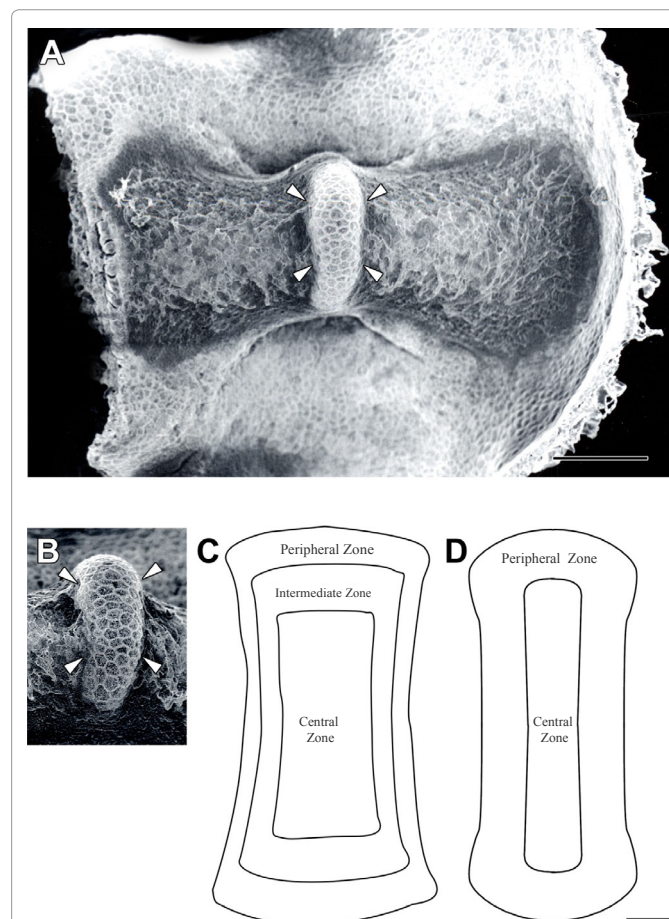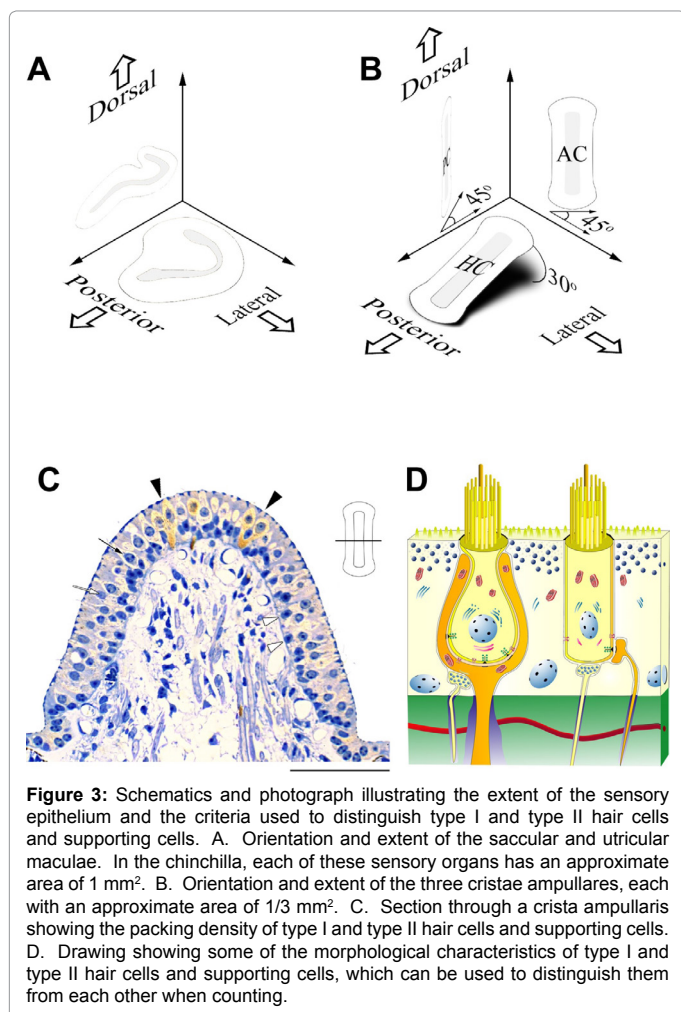

Figure 2: The boundaries and extent of sensory regions within the cristae ampullares. A. A scanning electron micrograph of a mouse vertical crista with the eminentia cruciatum indicated by the white arrowheads. B. The eminentia cruciatum is a nonsensory area of the epithelium, as shown in this higher magnification image. This region contains supporting cells and lacks hair cells. C. Boundaries of the three regions of the crista ampullaris based on a mathematical model (Fernández et al., 1988). The central zone (CZ) is the innermost zone, followed by the surrounding intermediate zone (IZ) and outermost peripheral zone (PZ). The three regions in this reconstruction are of equal area. D. Standardized boundaries from a crista as determined by the location of calretinin-labeled calyx afferents (Chapter 4). In this model, the intermediate and peripheral zones have been combined and the central zone is longer and narrower. Scale bars = 100 µm.

Figure 3: Schematics and photograph illustrating the extent of the sensory epithelium and the criteria used to distinguish type I and type II hair cells and supporting cells. A. Orientation and extent of the saccular and utricular maculae. In the chinchilla, each of these sensory organs has an approximate area of 1 mm². B. Orientation and extent of the three cristae ampullares, each with an approximate area of 1/3 mm². C. Section through a crista ampullaris showing the packing density of type I and type II hair cells and supporting cells. D. Drawing showing some of the morphological characteristics of type I and type II hair cells and supporting cells, which can be used to distinguish them from each other when counting.

dugong (a manatee-like mammal), gorilla, lemur, squirrel monkey, horse, cow, sheep, and humans – the similarity of such a structurally and functionally complex organ between these diverse species is striking. One of the earliest descriptions of labyrinth anatomy and function was published in a landmark paper by Szentágothai in 1952 [38].

Knowledge of the inner ear was furthered with the advent of the electron microscope in the 1950's and the careful preparation and fixation techniques necessary to resolve detail that came with it (Figure 2). After more than three centuries of work in the vestibular system, it became possible to examine the ultrastructure of the inner ear. In a series of papers by Wersäll and Engström in the 1950s, the fine structure of the sensory epithelium in the cristae and macular organs was described using the transmission electron microscope [39,40]. Scanning electron microscope studies of the inner ear have been applied since the late 1960's (Figure 3) [41-43].

Physiology of the Vestibular System

Functional studies in the vestibular system have not been lacking. Traditionally, vestibular physiology has been studied using two kinds of approaches – either mechanical stimulation of the semicircular canal or via hemi vestibulectomy (unilateral labyrinthine destruction). The basic anatomical features of the semicircular canals were first linked to their functional role by Flourens in 1842 [44]. A study by Ewald in 1892 described changes in muscle tone and postural reflexes as

a result of unilateral vestibulectomy [45]. Based on the utriculopetal and utriculofugal endolymph flow in the membranous labyrinth of pigeon semicircular canals, Ewald was able to form three laws: 1) eye and head movements occur in the direction of endolymph flow and in the same plane as the stimulated canal, 2) stimulatory motion through utriculopetal flow causes a greater response than utriculofugal flow in horizontal canals, and 3) utriculofugal flow of endolymph causes a greater response in vertical canals than utriculopetal flow. The utriculopetal direction is towards the utricular macula and the utriculofugal direction is away from this organ.

Nystagmus was described by Bárány in 1907 [46] as a response to rotational movements and the caloric stimulus test. Briefly, with the application of warm water to one ear in the caloric stimulus test, the presence of convection currents leads to a spontaneous decrease in discharge rate and a nystagmus in the direction of water application. Cold water has the opposite effect: spontaneous discharge increases and there is a nystagmus in the opposite direction. These tests would later form the mainstay of clinical vestibular tests.

Studies on the movement of the cupula were done using India ink in fish ampullae by Steinhausen in the 1920s [47-49]. Steinhausen was able to make fresh preparations of the crista ampullaris with the cupula intact. This allowed him to observe the behavior of the cupula in response to caloric and rotatory stimulation, experimentally simulate the effects seen by Ewald in 1892, and connect those effects to the nystagmus seen in the caloric test by Bárány in 1907. Electrophysiology studies of the vestibular system were first done by Ross and Lowenstein in the 1930s, who characterized the resting potential and effects of endolymph displacement in the frog and fish crista ampullares [50-52]. Changes in mammalian macular organ resting discharge rates in relation to head tilt were done by Adrian in 1943 and more detailed studies by Flock 1964 and Spoendlin in the 1960s [53,54]. Through these latter efforts, the physiological polarities of the sensory organs were detailed and the functional role of the striolar reversal line elucidated [53-55].

Future Directions in Vestibular Research

Since the basic morphological framework of the vestibular system was formed by Retzius, Lorente de Nó, Werner, Wersäll, and Lindeman, a great deal of work has been done in terms of elucidating the morphological, physiological, neurochemical, and pharmacological properties of the vestibular system in wild-type animals. However, studies on vestibular disorders are lacking. Part of the reason for this is the difficulty in choosing the appropriate animal model for human clinical disorders. The ideal is to choose an animal model that has similar morphological, physiological, neurochemical, and pharmacological traits to those found in humans; such an animal model exists in the squirrel monkey, but this resource is limited for obvious reasons.

As a result, investigators have turned to the mouse, rat, gerbil, guinea pig, chinchilla, toadfish, bullfrog, and other animals in order to develop a model for inner ear pathologies. Each of these animals involves a compromise due to differences between them and humans. For example, the significant hair cell regeneration seen in bullfrog and pigeon following the application of ototoxic aminoglycosides is not present in humans; the cause for this is unknown. An important calcium buffer in calyx terminals is found elsewhere in the mouse and rat, implying that the hair cells stained by calretinin antibody are not as differentiated as they are in higher mammals. Efferent studies in the gerbil are at odds with studies in the chinchilla, where the zonal boundaries of peripheral efferent innervation are different [56]. All of the rodents mentioned lack the morphological pattern found in human

tissue, such as the 5:1 ratio of type I to type II hair cells in the striolar region. This is significant due to the highly specialized ending on type I hair cells, the functional implications of having a higher proportion of calyx afferents, and the resulting differences in central processing.

Due to the lack of a paragon, current clinical research takes advantage of all of these species. It is difficult for investigators who do physiology in the bullfrog to apply their findings in mammals, and vice versa. The resulting confusion makes the formation of a mainstay in treatment difficult and incomplete. However, many of these problems are endemic to other clinical specialties that rely on animal models. What is uniquely affecting clinical vestibular science is the lack of transgenic animals that express phenotypes for vestibular disorders, the relative efficacy of treatment of certain vestibular disorders, the lack of studies on pathological samples obtained from human material, the difficulty in obtaining well-fixed human material for study, and the difficulty in applying basic science findings in a clinical setting.

An animal model that mimics human vestibular disease at the genetic level is critical for precisely understanding the changes that occur during the progression of the disease. It would allow investigators to see the onset of the disease and trace it back to its cause by following morphological, neurochemical and functional changes. With the refined methods of tissue dissection and fixation available in animal models, this approach would alleviate the need for obtaining well-preserved human pathological samples.

Once underlying causes of vestibular disorders are well-characterized, treatment regimens could be explored in these animal models that would never be tolerated in a clinical setting. Transgenic models provide a path around the difficulty in applying certain treatments to humans through gene therapy. For example, a common treatment for vestibular disorders is to simply remove the offending labyrinth. While humans can live with only one labyrinth, one eye, or one arm, no one chooses this unless it is the last resort. The difficulty in surgical intervention in Ménière's disease, especially in accessing some of the deeper recesses of the inner ear, could be minimized. Recent discoveries point to a familial pattern of disorders for Ménière's disease, though additional studies are needed to determine the haplotype through linkage analyses [57]. Early data indicates that Ménière's disease may be carried by an autosomal dominant gene, and that the offending gene potentially carries a mutation similar to that found in spinocerebellar ataxia, that is, a trinucleotide expansion that disrupts translation [58]. Gene therapy promises to be an alternative to the use of invasive techniques in treating vestibular disorders.

Conclusion

In the last two decades, work in the vestibular system has taken the path of elucidating the morphophysiology of the efferent innervation and neurochemically characterizing the afferent and efferent innervation [59-62]. Through a combination of immunohistochemical and molecular biology approaches, the neurotransmitters, channel proteins, signal transduction cascades, and related proteins are being determined [63]. The recent completion of the Human Genome Project and the mapping of genes related to vestibular development may make it possible to better understand the development process of the vestibular system and to correct morphological disorders during ontogeny before they become a problem.

References

1. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB (2009) Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. Arch Intern Med 169: 938-944.

2. Casserii GC (1610) De Auris Auditus Organi Structura. Frankfurt.

3. Du Verney M (1683) Traite de L'Organe de L'Ouie.

4. Valsalva AM (1704) De Aure Humana Tractatus.

5. Du Verney M (1730) Tractatus de Organo Auditis: Continens Structuram Usam et Morbos Omnium Auris Partium.

6. Du Verney M (1731) Traité de L'Organe de L'Ouie: Contenant la Structure les Usages & les Maladies de Toutes les Parties de L'Oreille.

7. Scarpa A (1789) Anatomicae Disquisitiones de Auditu et Olfactu, Ticini.

8. Fabricius A (1600) Hieronymi Fabricii ab Aquapendente De Visione Voce Auditu, Venetiis.

9. Fabricius A (1613) Tractatus Anatomicus Triplex Quorum Primus De Oculo Visus; Secundus De Aure Auditus; Tertius De Laringe Vocis Admirandam Tradit Historiam Actiones Utilitates, Oppenheim.

10. Klein JT (1740) Historiae Piscium Naturalis Promuendae Missus Primus de Lapillis Eorumque Numero in Craniis Piscium Cum Praeatione de Piscium Auditu, Gedani.

11. Monro A (1785) The Structure and Physiology of Fishes Explained and Compared With Those of Man and Other Animals. Edinburgh.

12. Scarpa A (1772) De Structura Fenestrae Rotundae Auris et de Tympano Secundario Anatomicae Observationes. Societatem Typographicam Mutinae.

13. Retzius G (1881) Das Gehörorgan der Wirbelthiere. I. Das Gehörorgan der Fische und Amphibien, Der Centraldruckerei Stockholm.

14. Retzius G (1884) Das Gehörorgan der Wirbelthiere. II. Das Gehörorgan der Reptilien der Vogel und der Saugethiere. Der Centraldruckerei Stockholm.

15. Retzius G (1894) Die endigungsweise des gehörnerven bei den reptilien. Biologica Untersuchung.

16. Cajal SR (1889) Conexión general de los elementos nerviosos. In La Medicina Práctica, Madrid.

17. Golgi C (1908) La doctrine du neurone. In Les Prix Nobel en 1906. P.A. Norstedt and Söner Stockholm.

18. Gerlach J (1848) Handbuch der allgemeinen und speziellen gewebelehre des menschlichen körpers für ärzte und studierende. In Erstauflage. Mainz editor. Eingedruckten Holzschnitten Janitsch.

19. Gerlach J (1874) Das verhältniss der nerven zu den willkürlichen muskeln der wirbelthiere. In Histologische Untersuchung. F.C.W. Vogel Leipzig.

20. Ayers E (1892) Über das periphere verhalten des gehörnerven und den wert der haarzellen des gehörorgans. Journal of Morphology 6.

21. Krause R (1896) Die endigungsweise des nervus acusticus im gehörorgan. Verhandlungen der Anatomischen Gesellsehaft.

22. Niemack J (1892) Maculae und cristae acusticae mit Ehrlich's methylenblau-methode. Anatomische Hefte 2: 205-234.

23. Ehrlich P (1882) Aus dem verein fiir here meditin zu Berlin. Sitzung vom 1. Deutrcbe Wtedizinische Wocbenschift 8: 269-270.

24. Kolmer W (1904) Über die endigungsweise des nervus octavus. Zentralblatt für Physiologie 18: 20.

25. Lorente de Nó R (1926) Études sur l'anatomie et la physiologic du labyrinthe de l'oreille et du VIII e nerf. Peuxieme partie. Queldues donnees au sujet de l'anatomie des organes sensoriels du labryrinthe. Trav Laboratorio Rech Biológicas Universidad de Madrid 24: 53-153.

26. Kato H (1911) Über die peripherischen endigungen des nervus acusticus beim Leucopsarion petersi hilgendorf. Folia Neurobiologica 5: 424-435.

27. Corti A (1851) Recherches sur l'organe de l'ouïe des mammifères par le marquis. Zeitschrift für Wissenschaftliche Zoologie 3: 1.

28. Kaiser O (1891) Das Epithel der Cristae und Maculae acusticae. Archiv für Ohren Nasen und Kehlkopfheilkunde Vereinigt mit Zeitschrift für Hals Nasen und Ohrenheilkunde 32: 181.

29. Cajal SR (1904) Asociación del nitrato de plata con el embrionario para el estudio de los focos motores y sensitivos. Trabajos del Laboratorio de Investigaciones Biológicas 3.

30. Cajal SR (1903) Asociación del método del nitrato de pista con el embrionario para el estudio de los focus motores y sensitivos. Trabajos del Laboratorio de Investigaciones Biológicas 3: 83.

31. Cajal SR (1908) Terminación periférica del nervio acustico de las aves. Travaux du Laboratoire de Recherches Biologiques de l'Université de Madrid 6: 161-176.

32. Cajal SR (1908) Sur un noyau special du nerf vestibulaire des poisons et des oiseaux. Travaux du Laboratoire de Recherches Biologiques de l'Université de Madrid 6: 1-21.

33. Alexander G (1899) Zur anatomie des ganglion vestibulare. Sitzungsberichte der Heidelberger Akademie der Wissenschaften Mathematisch-Naturwissenschaftliche Klasse 108: 449 467.

34. Wittmaack K (1904) Über markscheidendarstellung und den nachweis von markhüllen der ganglien im acusticus. Archiv fur Ohren Nasen und Kehlkopfheilkunde Vereinigt mit Zeitschrift fur Hals Nasen und Ohrenheilkunde 61: 18-23.

35. Poljak S (1927) Die nervenendigungen in den vestibulären sinnesepithelien bei säugetieren. Zeitschrift fur Anatomie und Entwicklungsgeschichte 84: 704.

36. Werner CF (1936) Über den einfluss der konzentration und des osmotischen "Druckes" der fixationslösung und die forderung der isotonie. Zeitschrift für Zellforschung und mikroskopische Anatomie 25: 341-352.

37. Gray AA (1907) The Labyrinth of Animals. I and II. J and A Churchill London.

38. Die Rolle der einzelnen Labyrinthrezeptoren bei der Orientation von Augen und Kopf im Raume (Unter Mitwirkung von A. Gömöry, R. Scháb, J. Sas) Bp.: Akadémiai Kiadó, 1952

39. WERSALL J (1954) The minute structure of the crista ampullaris in the guinea pig as revealed by the electron microscope. Acta Otolaryngol 44: 359-369.

40. Wersall J (1956) Studies on the structure and innervation of the sensory epithelium of the cristae ampulares in the guinea pig; a light and electron microscopic investigation. Acta Otolaryngol Suppl 126: 1-85.

41. Lim DJ (1969) Three dimensional observation of the inner ear with the scanning electron microscope. Acta Otolaryngol Suppl 255: 1-38.

42. Harada Y (1983) Atlas of the Ear. MTP Press Limited Lancaster England.

43. Harada Y (1983) Ultrafine structure of the otoconial membrane. Adv Otorhinolaryngol 30: 258-263.

44. Flourens P (1842) Recherches Expérimentales sur les Propriétés et les Fonctions due Système Nerveux Dans les Animaux Vertebras. Paris Crevot.

45. Ewald JR (1892) Physiologische Untersuchungen uber das Endorgan des Nervus Octavus. Bergmann Wiesbaden.

46. Bárány R (1907) Physiologie und Pathologie des Bogengang-apparates beim Menschen: klinische studien. Vienna Deuticke.

47. Steinhausen W (1927) Über Sichtbarmachung und Funktionsprüfung der Cupula terminalis in den Bogengangsanipullen des Labyrinthes. Pflügers Archiv European Journal of Physiology 217: 747 755.

48. Steinhausen W (1931) On the independent movement of the cupula in the semicircular canal ampulla of the labyrinth. Pflügers Archiv European Journal of Physiology.

49. Steinhausen W (1933) Über die beobachtung der cupula in den bogengangsampullen des labyrinths des lebenden hects. Pflügers Archiv European Journal of Physiology 232: 500-512.

50. Ross DA (1936) Electrical studies on the frog's labyrinth. J Physiol 86: 117-146.

51. Lowenstein O (1936) The equilibrium function of the vertebrate labyrinth. Biol Rev11: 113-145.

52. Adrian ED (1943) Discharges from vestibular receptors in the cat. J Physiol 101: 389-407.

53. Flock A (1964) structure of the macula utriculi with special reference to directional interplay of sensory responses as revealed by morphological polarization. J cell biol 22: 413-431.

54. Spoendlin HH (1964) Organization Of The Sensory Hairs In The Gravity Receptors In Utricule And Saccule Of The Squirrel Monkey. Z Zellforsch Mikrosk Anat 62: 701-706.

55. Lowenstein O, Wersäll J (1959) A functional interpretation of the electron microscopic structure of the sensory hairs in the cristae of the elasmobranch Raja clavata in terms of directional sensitivity. Nature 184: 1807.

56. Purcell IM1, Perachio AA (1997) Three-dimensional analysis of vestibular efferent neurons innervating semicircular canals of the gerbil. J Neurophysiol 78: 3234-3248.

57. Mancini F1, Catalani M, Carru M, Monti B (2002) History of Meniere's disease and its clinical presentation. Otolaryngol Clin North Am 35: 565-580.

58. Oliveira CA1, Bezerra RL, Araújo MF, Almeida VF, Messias CI (1997) Menière's syndrome and migraine: incidence in one family. Ann Otol Rhinol Laryngol 106: 823-829.

59. Goldberg JM, Fernández C (1980) Efferent vestibular system in the squirrel monkey: anatomical location and influence on afferent activity. J Neurophysiol 43: 986-1025.

60. Dechesne C, Raymond J, Sans A (1984) The efferent vestibular system in the cat: a horseradish peroxidase and fluorescent retrograde tracers study. Neuroscience 11: 893-901.

61. Lysakowski A, Goldberg JM (1997) A regional ultrastructural analysis of the cellular and synaptic architecture in the chinchilla cristae ampullares. J Comp Neurol 389: 419-443.

62. Lysakowski A (1999) CGRP shows regional variation in efferent innervation of chinchilla vestibular periphery. Proceedings of the Society of Neuroscience 25: 1670.

63. Wackym PA, Balaban CD (1998) Molecules, motion, and man. Otolaryngol Head Neck Surg 118: S16-24.