ISSN: 2641-1911
DOI: 10.33552/ANN.2021.10.000728
Archives in Neurology & Neuroscience
Iris Publishers

Review Article

The Link Between Brain and Auditory System and Possible Role of Vestibular System in Hearing System as a Second Middle Ear and the Role of Melanocytes and/or Neuromelanin in this Process

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Received Date: March 10, 2021

Published Date: March 23, 2021

Abstract

Backward Auditory input pathways of Sound hypothesis describes that sound might be transferred from our Skin and eyes to the Inner Ear and the External Auditory Canal is not the only input of Sound, The Cochlea receives the sound from two separate directions Forward Auditory input pathway which are the Signals reach out to the cochlea from the External ear canal and the second direction Backward Auditory input pathways which are the signals transfer from our Skin and eyes and approach to the cochlea. The cochlea receives the sound from both directions and organizes and transfers them to the Brain for the ultimate processing.

We deal with this subject by explaining

A: General features of Melanocytes, Melanin and Neuromelanin

B: Those parts of the Brain contain Neuromelanin and their link with Vestibular system

C: Vestibular System, Third Window Disorders and Third Window Mobile Hypothesis vs second middle ear disorders hypothesis

D: Possible implications of Vestibular system and Neuromelanin/Melanin in Backward Auditory Input pathways of sound

Keywords: Otosclerosis; Meniere's syndrome; Forward and backward auditory input pathways; Melanin; Neuromelanin; Melanocytes; Third window disorders; Vestibular System; Sensorineural hearing loss; Cochlea; Conductive hearing loss; Semicircular canals; Utricle; Saccule; Round Window; Oval Window

Melanocytes and Neuromelanin

Skin's Melanocytes are situated on the Stratum Basale of the skin's epidermis and they are considered melanin-producing neural crest-extracted cells. They are also all over the body such as the uvea which is the middle layer of the Eye, the Cochlea and Vestibular System, vaginal epithelium, Leptomeninges, bones, and heart [1,2]. Melanin is a dim pigment and one of its roles is in Skin color. When the Melanin is synthesized. It is included in a specific multinucleate so called melanosomes which is delivered to adjacent keratinocytes to produce pigmentation. Melanocytes and Melanin have a function in the immune system also protection against UV radiation and many other roles [3,4]. Melanocytes generate melanin through a procedure called melanogenesis, this pigment is noticed in many parts of the body. The pigmentation which initiates from Oxidation of already existing Melanin is different from this

Melanogenesis result to pigmentation [5]. Melanogenesis contains basal and actuated levels; low basal levels of melanogenesis are usually seen more in people with brighter skin's color. Elevation in melanogenesis has been observed in exposure to UV-B radiation. Physiologically melanogenesis protects the hypodermis, which is the layer under the skin, from damage by UV-B radiation. The Melanin absorbs the UV-B light by its dark color and does not let it passes through the Epidermis [6]. In a square millimeter of skin almost 1000 to 2000 melanocytes could be found or almost five to ten percent of the cells in the deepest part of the epidermis. The length of the Melanocytes is usually 7 Micrometer, however, their size can be diverse [7,8]. The amount of the Melanocytes is not in charge of the skin color between dark and brighter skin people, but the level of the quantity of the melanocytes also amounts of eumelanin and pheomelanin is involved in this procedure [9].

Melanocytes are believed to have a function in Immune system, and they are considered sort of Immune cells however their function in Immune system is not completely understood so far [10]. Protecting the body by ingesting harmful foreign particles, branched feature look like, Cytokines producing are some of the same features between Melanocytes and Dendritic cells [11]. albeit both melanocytes and Dendritic cell have some similarities, but they are not completely identical. The cell lineages which they are derived from are completely different [11]. Presenting antigen and producing Cytokine are some of the function of melanocytes in immune system [12-14].

IL-1, IL-3, IL-6, IL-8, TNF-α, and TGF-β are Proinflammatory cytokines which can be produced by melanocytes [15]. Besides, cytokines discharged by other nearby immune cells stimulate the cytokine's production by melanocytes [15]. Melanocytes are the protector's cells against harmful pathogens. Melanocytes utilize their dendrites to communicate with cells in other layers other than the Stratum basale [17]. Melanocytes fight against any pathogens which come to the epidermis [17]. Melanocytes are in link with both Keratinocytes and Langerhans cells which both are strongly phagocytic in response to the immune system.

It is observed that Melanogenesis could be changed by numerous stimuli, albeit this process and how it works is unknown right now. The Melanoblast is the Melanocyte precursor's cell. Stem cells are located in the projection section of the external deepest part of hair follicles in adults. The stem cells are actuated when a hair is lost and regrows again. Both keratinocyte precursors and melanoblasts are the transformation products of these stem cells and they enrich both hair and skin. There is also proof that in cutaneous nerves Melanocytes stem cells are existing, with nerve signals resulting them to convert into melanocytes for the skin [17].

Neuromelanin

Neuromelanin (NM) is a dim pigment that exists in some parts of the brain that is mainly associated to melanin. The substantia nigra pars compacta, locus coeruleus, ventrolateral Reticular Formation Medulla Oblongata are those parts of the brain which NM can be found in large amounts [17]. Neuromelanin provides typical brain sections, which mentioned earlier definite color. It is a branch of melanin and looks like the other types of melanin which is found in peripheral sections. It is insoluble in organic consolidations, also it can be characterized by silver staining. The name of the Neuromelanin is because of its role also the feature of color's changes that emerge in those substances which contain the NM. NM carries dark and hazel pigmented spots. NM is seen to amass in aging, considerably after the first 2 or 3 years of life. The reason of this is probably because of the protection role of NM against iron- induced oxidative stress in Substantia Nigra [18,19].

Neuromelanin is observed in more quantities in humans compared to non-human primates [17]. The concentration of the Neuromelanin is increased with the aging process probably because of the protection of the neurons. It is believed that in Parkinson disease neurodegeneration of the Neuromelanin which contains some Neurons and cell death in substantia nigra is involved in this disease. Probably Oxidative stress in this region is the reason for the cell death and supposedly the motor symptoms in this disease is because of this Oxidative stress. The Neuromelanin might be able to revive this Oxidation. The quantity of the Neuromelanin of Substantia Nigra is usually 50 percent less in patients who suffer from Parkinson disease compared to normal individuals. The Neurodegeneration of the Neuromelanin in Pars Compacta and Locus Coeruleus also involved in this disease and has been proved and observed by imaging of the Neuromelanin on these parts of the Brain [18]. Neuromelanin could prevent the Neurodegeneration by binding neurotoxic and/or toxic metals [18].

Purkyně was the first scientist who expressed black pigments in Substantia Nigra in 1838 and Lillie described the Neuromelanin in 1957 and on that time they believed that Neuromelanin physiologically has no role but now it is scientifically proved that they are cell protectors of some parts of the Brain also their link with Parkinson disease and because of this possibility scientist strongly are doing research in Neuromelanin [19]. Melanocytes and Neuromelanin also have the ability to absorb the mechanical energy such as Sound and light and transform the light to sound and vice versa. They have an important function in hearing system which will be explained later in this paper [20-29].

Neuromelanin-Locus coeruleus

The posterior area of the rostral pons in the lateral floor of the fourth ventricle is a section of the brain which Locus Coeruleus (LC) is located. It is in the brainstem and a branch of the Reticular activating system. One of its functions is controlling the panic and Stress [30].

LC is the major source of the Norepinephrine along with adrenal medulla which supplies the Norepinephrine directly to the blood [31]. Medium size Neurons could be found in LC. The color of the LC is blue and it is because of the Melanin or pigmented

cells inside the neurons of the LC. LC is a nucleus in the pons and is strongly pigmented and because of this feature another name of the LC is the Nucleus Pigmentosus Points. The Neuromelanin of the LC is similar to the dark Neuromelanin dopamine base of the Substantia Nigra and Polymerization of noradrenaline is structured the Neuromelanin of the LC [32]. The quantities of the pigmented neurons in LC are almost twenty two thousands to fifty one thousands and their size is different from 31,000 and 60,000 μm3. This is apply to humans between the age of 19 to 79 years old [33].

The LC has many projections to many parts of the brain. The LC is involved in Arousal and sleep awake cycle by its excitatory effect of the Neuromelanin [33,35]. Some other functions of the LC are the homeostatic control center of the body, Attention, memory, behavioral and/or cognitive elasticity, creativity, cognitive control, neuroplasticity, emotions, posture and balance and so on. Since the LC is a branch of reticular activating system then it is inactivated during rapid eye movement stage of the sleep [34,36-38].

It is believed that there is a link between the LC and many pathologies such as Alzheimer, Parkinson, depression and so on [35]. There is a high possibility of the link between Norepinephrine dysfunction of the LC and many cognitive and neuropsychiatric disorders such as PTSD, ADHD or other cognitive disorders which mentioned earlier [36,37]. The LC is also involved in some other disorders as well such as progressive supranuclear palsy, Pick's disease, Down syndrome [38]. The Locus Coeruleus has a tremendous role in Audio/vestibular System, The LC likely standby the Cochlea and/ or Vestibular system during sleep by its inactivation through Reticular Formation and Reactivate it again during arousal. LC and its connections are responsible for Pupil dilation following Auditory Stimuli. Many studies have been done recently regarding Pupil dilation following Auditory stimuli which can be used for the diagnosis of the Hidden Hearing Loss (cochlear Synaptopathy) also it can be used for the diagnosis of the hearing loss as an objective test very Soon [39].

Neuromelanin, Substantia Nigra- Pars Compacta

The Midbrain is a branch of the Brain which Substantia nigra (SN) is located and Pars Compacta (PC) is a part of SN so it is called Substantia Nigra Pars Compacta (SNPC) The SNPC contains Dopaminergic neurons and the dark pigmented Neuromelanin are existed in this section of the brain. The neurons of the SNPC are not involved in movement directly but it organizes the Striatum and by this management role it is involved in movement indirectly so dysfunction on Pars Compacta neurons have a huge impact on movement which can be seen in patients who suffer from Parkinson disease [40]. Parkinson disease could be sometimes genetic or secondary to infections or toxins [41]. Dysfunction on this section of the brain may also involve schizophrenia and/or addictive conduct as this part of the brain is involved in reward and pleasure as well. Spatial learning and temporal processing, inspection of the environment and location in space also part of the memory, sleep wake cycle are other functions of the PC [41-44]. Substantia Nigra is a branch of Basal Ganglia and it has a tremendous role in the Hearing and Balance system. Basal Ganglia implicated in speech categorization and speech recognition. Patients who suffer from sensorineural hearing loss and also have trouble understanding nonnative accent likely have dysfunction in Basal Ganglia. Vestibular System is probably involved in Parkinson Disease as well because of its link and connections with Substantia Nigra [41,42,43,46].

Neuromelanin- Ventrolateral Reticular formation- Medulla Oblongata

The reticular formation is a region of the Brainstem and its neurons located from top of the Midbrain to the bottom section of the Medulla Oblongata [40-42]. Somatic motor control, maintaining tone, balance, and posture typically during body movements, imparts eye and ear signals to the cerebellum so that the cerebellum can combine visual, auditory, and/or vestibular stimuli in motor coordination. Activation the eyes to trace and fixate objects, modulation of breathing and swallowing, Cardiovascular control, modulation of the pain. Sleep and states of consciousness such as alertness and sleep, Habituation are some physiological functions of the Reticular Formation [42-51].

Medulla Oblongata

The medulla oblongata or medulla is a section of the brainstem [52]. It is located near to the Cerebellum. (Anterior-inferior part of the Cerebellum) [53]. Physiologically it is in charge of Vomiting, Sneezing, coughing, swallowing. Cardiac, respiratory, breathing, heart rate, blood pressure, sleep wake cycle [54-58].

There is a significant link between Medulla and the Audio / vestibular system. Vomiting following Vestibular dysfunction also increasing blood pressure following Vestibular loss are perhaps because of the link between Medulla with Audio -Vestibular system. We have seen many patients during our clinical experience without having any history of blood pressure which their blood pressure increased following Vestibular disorders although other reasons is proposed for this such as hypertension following stress secondary to Vertigo but now a days the function of Vestibular system in regulating blood pressure is observed [59].

Meninges- Leptomeninges

The meninges consist of three different sections in human, dura mater, the arachnoid mater and the pia mater. Between the arachnoid mater and pia mater which is the subarachnoid space the Cerebrospinal fluid could be observed. Meninges function is to protect the Central Nervous system. So-called Leptomeninges are arachnoid and pia mater together [60]. The arachnoid mater or arachnoid membrane is the middle part of the Meninges, it is called Arachnoid membrane because it looks like a spider web. It is consisted of fibrous tissue as well as the pia mater, has an external covering of firmly filled prone cells, establishing the arachnoid barrier [61]. Arachnoid Trabeculae is a complex of filament which

proceed from the arachnoid through the subarachnoid space to combine with the pia mater. There is a collagen on exterior side of arachnoid barrier which is responsible for essential meningeal barrier across the cerebrospinal fluid and subarachnoid space as well as the blood circulation in the dura [62]. The pia mater is a sensitive and narrow membrane. It covers the meningeal section of the brain and tightly attach to the brain's exterior part as well as spinal cord. It is located following the gyri and sulci. It consists of fibrous tissue extended on its external layer by some cells believed to be impervious to fluid. It is believed that Leptomeninges produces the beta-trace protein or prostaglandin D2 synthase, which is the main cerebrospinal fluid protein. The Leptomeninges are in connection with Semicircular canals through the CSF and /or Perilymph via Melanocytes which can be found in Leptomeninges as well as Semicircular Canals in the Vestibular system [63-70].

Vestibular system, Third Window Disorders and Third Window Mobile Hypothesis vs Second Middle Ear Disorders Hypothesis

The vestibular system is physiologically involved in balance and /or spatial detection. It contains two different sections, the first section is Semicircular canals (Superior, posterior, horizontal) Superior and posterior canals are considered vertical semicircular canals. The lateral canals are involved in head's rotation on vertical axis for example during gyrations, on the other hand the Superior and posterior canals are involved in longitudinal and/or coronal plane rotations for example during nodding or circular handspring. The second section of the Vestibular system is Otoliths (Utricle, Saccule) which is in charge of linear acceleration [71,72]. The muscles receive the signal from Vestibular system which give us the ability to upright and control the posture [73-86].

The link between the brain and Vestibular system lead to the comprehension of the body's dynamic and/or Kinematics which eventually helps us to figure out the position and/or acceleration from time to time [76].

Studies showed both Semicircular canals and Otolith Organs are involved in Hearing system as well, Sudden deafness following Benign paroxysmal positional vertigo (BPPV), Abnormal Video Head Impulse test and Caloric test in Idiopathic Sudden Deafness, Otolith dysfunction in High Frequencies hearing loss and Profound Sensorineural Hearing loss are some examples of their significant link with Auditory system [87-89].

Third Window Disorders are referred to those pathologies of the Inner ear which typically cause Conductive or Mixed Hearing loss, in normal ears there are two Widows, Round and Oval Window. According to the Third Window mobile hypothesis the Third window caused by these pathologies such as Superior, Posterior, Lateral Semicircular Canals dehiscence, Large Vestibular Aqueduct Syndrome and so on is the reason for the Conductive hearing loss on these disorders. in consonance with this hypothesis because of abnormal Third Window caused by these pathologies transmission of the sounds from the Oval Window to the Round Window is disrupted and acoustic energy cannot reach out to the Round window properly and eventually less sound energy accessible to the hair cells [90-93]. If Third Window Mobile hypothesis is completely true then we should expect less Air bone gap (Conductive Hearing Loss) in concomitant Superior Semicircular Canal dehiscence (SSCD) and Otosclerosis compare to patients who suffer from SSCD only because the stiffness effect following Otosclerosis conquer the Hyper mobility induced by the Third Window but most case reports in Concomitant SSCD and Otosclerosis showed maximum Air Bone Gap also the Round Window reinforcement surgery technic must make the hearing loss lessen or cure but studies showed this surgery technique can make the symptoms alleviated but the hearing loss following SSCD could not be changed after surgery and even Round window complete occlusion technic causes the situation worse in some case studies. It seems that physiologically the Vestibular system is the second middle ear and Vestibular system receives the auditory information as well through the engagement between Vestibular Melanocytes and CNS Melanocytes (Melanin, Neuromelanin) and delivers the information to the cochlea. (Second Middle ear disorders hypothesis) [93-97].

Discussion

The Brain Functional Imaging studies such as fMRI and Functional Near-infrared spectroscopy (FNIRS) showed that the Hearing or Auditory system is a Multimodal system [98]. Vision/eyes and, Tactile/skin are involved in the hearing system [98,99]. Echolocation in some animals and humans also Gesturelocation (ability of some blindness people to do the gesture and move their hand frequently to specific directions and identify the objects size and shape) are some examples of the link between these senses with each other [123,124]. It seems that Utricle and Saccule receive the auditory information from two different directions forward auditory input pathway and Backward Auditory input pathways [100]. In forward auditory input pathway auditory signals come to the external ear canal, Tympanic Membrane, Ossicles and eventually Utricle and Saccule and in backward Auditory input pathways of sound signals collected from skin/Tactile and vision/eyes by Central Nervous System (CNS) Melanocytes and Neuromelanin. The CNS Melanocytes are in connection with Vestibular and/or Cochlea's Melanocytes. The Neuromelanin of the locus coeruleus, Pars Compacta, Ventrolateral Reticular formation-Medulla Oblongata, Leptomeninges and their connections are involved in transmission of the sound from Skin/tactile and Vision/eyes to the Semicircular Canals and eventually Utricle and Saccule. In the backward auditory input pathway of sound, there is a high possibility that Melanocytes and Neuromelanin pass the auditory information through Gap Junctions [107]. In Utricle and Saccule the auditory information will be separated from Vestibular information and the auditory information from two different directions (forward auditory input pathway and backward auditory input pathways) will be combined and eventually the combined information will be

delivered it to the cochlea [100-106]. Melanin and pigmented cells have been observed around the Round Window Membrane (RW) [108]. The auditory signals which come through the forward and backward auditory input pathways absorb by RW membrane by its outward movement following the vibration of the oval window also its pigmented cells and conduct them to the cochlea. The Round Window pumps all the combined auditory information from two directions (forward and backward auditory input pathways) and delivers it to the Cochlea [108]. both cochlear conductive hearing loss and Sensorineural hearing loss have been reported in RW Pathologies. Type of the hearing loss depends on the site and degree of the lesion in RW membrane and its surrounding [109,110]. Cochlear conductive hearing loss also has been reported in Meniere's disease, although another hypothesis is proposed but the Vestibular organs dysfunction because of stiffness caused by hydrops might be the reason for the conductive component hearing loss in this disease [111]. Albeit Conductive or Mixed Hearing loss is more common in Superior, posterior, lateral Semicircular Canals Dehiscence and Large Vestibular Aqueduct Syndrome but Sensorineural hearing loss has been reported as well so type of the hearing loss depends on the site and degree of the lesion as Vestibular system contains pigmented and transitional cells [112-115]. Pupil Dilation following auditory stimuli has been observed [116]. Ocular and CNS Melanin whether absorb the Sound as well as light and transfer it to the Semicircular canals, Utricle and Saccule and eventually the cochlea or Ocular and CNS Melanin transform the sound to the light and then transmit the light to the Semicircular Canals, Utricle and Saccule and eventually the cochlea and sense of hearing occurs following Optogenetic like stimulation and/or genetic engineering like [117,118]. It seems that Semicircular Canals have the ability to detect the sound from different directions through the connection of their Melanocytes and CNS melanocytes and act as an Antenna. In some animals like Cheetah, which is one of the fastest creature on earth, the Semicircular Canals are much larger than human as well as more variety of Melanocytes which give the ability to detect any movement of other creatures also the amazing speed and balance system and ability to zoom precisely on the target [119,120].

Conclusion

Engagement of the subcortical area of the brain which mentioned earlier in backward auditory input pathways of sound is more prominent than cortical areas. It seems that the subcortical areas of the CNS are the coordinators of the hearing system between Peripheral sections and cortical areas. It is likely that part of the Vestibular system physiologically is responsible for transmitting part of the auditory information to the Cochlea. Melanocytes all over the body are in link and connection with each other and this is one of the reasons or hypotheses of the hearing loss in renal failure and/or Hearing loss in heart disorders [121,122]. Investigations and research regarding the Melanocytes and Neuromelanin not only open the new doors for the treatment of hearing loss, it can open the doors for the treatment of many other disorders as they are all over the body also they are in link with many Pathologies. The Vestibular system has a tremendous role in the auditory/Hearing system. The Cochlea and Vestibular system are actually one system that work together. There is no sense of hearing without Vestibular system and Vice Versa. It seems that the Cochlea receives the sound from two different directions, Forward auditory input pathway and backward auditory input pathways. The Cochlea is the ultimate target of all the auditory information from both forward and backward auditory input pathways of sound and after initial coding and processing it sends the information to the Brain for the terminal processing [123-125].

Acknowledgments

None.

Conflicts of Interest

The author declares that there is no conflict of interest to disclose.

Funding

None.

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