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Homocysteinemia and Otology

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8.1 Homocysteinemia and Otology

The cochlea is a perfect example of the matrix effects of homocysteinemia as most of its effects are exhibited through modulation of the extracellular matrix in this organ. To be able to clearly understand these effects, it would be pertinent to give a short description of this organ.

The cochlea is a convoluted compartmentalized snail shell-like structure with its lumen containing three fluid-filled compartments. In two of these, the fluid functions as a pressure transmitter, perceiving the sound waves as pressure changes and transmitting them to the third compartment which houses the very sensitive organ of Corti. Here the pressure changes are converted to electrical impulses which then travel along the auditory nerve to the brain. The organ of Corti is comprised of very specialized cells—the hair cells—which are present in two layers (the outer and the inner layers) embedded in an equally specialized extracellular matrix (ECM). These hair cells along with the ECM constitute the actual sound impulse detectors and transmitters of our ears. Any alteration in these cells or this matrix would therefore negatively impact our ability to deal with the impulses perceived. Since homocysteinemia alters the ECM through the MMPs, especially MMP-9, it would follow that homocysteinemia impacts hearing as well. Also, as discussed in the section on neurological effects of homocysteinemia, hearing could also be impaired by the effect of homocysteinemia on the neurons associated with the function of hearing (Fig. 8.1).

Kundu et al. demonstrated that as compared to their wild-type counterparts, CBS+/− mice exhibited elevated levels of MMPs 2, 9 and 14 and decreased concentrations of TIMPs 1, 2 and 3 in the brain and cochlea. Also, since it is known that acute as well as age-related hearing loss occurs as a sequel of altered blood flow to the inner ear, they proposed that homocysteinemia probably affects the cochlear microcirculation in the same way that it affects the BBB, as described in the previous sections.

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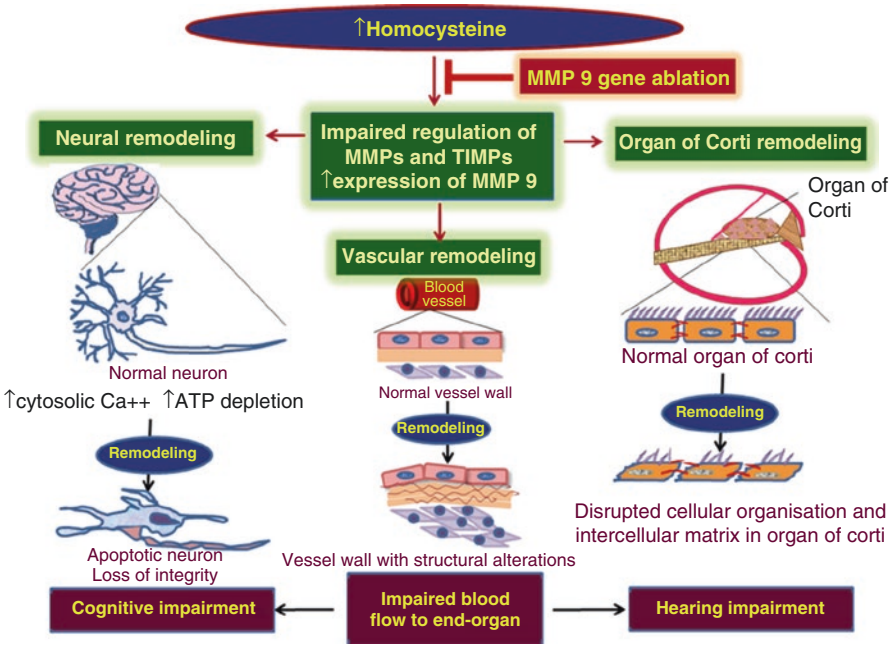

Fig. 8.1 Mechanism of homocysteinemia-induced MMP-9 causing vasculo-cerebral and vasculo-cochlear remodelling

So far as the role of MMPs and TIMPs is concerned, in normal hearing they maintain a very fine balance. This was exemplified by Setz et al. (2011) who demonstrated that gentamicin (ototoxic, specifically for the organ of Corti) increased the expression of MMPs 2 and 9 in the organ of Corti, whereas exposure to MMP inhibitors resulted in hair cell death in the wild-type mice (those without homocysteinemia). Thus, it emerged that the proportionate expression of MMPs and TIMPs is all-important for normal hearing.

The cochlea actually lends itself to a variety of alterations due to trauma and homocysteinemia as there are several types of tissue within this structure (Thome et al. 1984). Hu et al. (2012) demonstrated the differential response of apical versus basal epithelium of cochlea to insult; the apical expression of MMPs was more upregulated as compared to that in the basal region. The apex transduces low-frequency sounds, whereas hearing of the higher frequencies is attributed to the basal region. Hence, hearing loss due to homocysteinemia starts in the lower frequencies as opposed to age-related hearing loss (presbyacusis) which starts at the higher frequencies. Another reason is that due to the apex being the distalmost in terms of blood supply, it is the first to get affected by aberrations of the microcirculation in the stria vascularis, and hence low-frequency hearing loss precedes high-frequency loss due to homocysteinemia.

Martinez-Vega et al. (2014) demonstrated that C57BL/6 mice (normal) fed with a folate-deficient diet for 8 weeks had sevenfold lower circulating folate levels and threefold higher circulating homocysteine levels. These folate-deficient mice exhibited severe hearing loss as measured by the auditory brainstem recordings and apoptotic cochlear cells. In the cochlea, the enzymes of homocysteine metabolism were reduced, and there was a 30% increase in protein homocysteinylation. Also, redox stress was evident in the form of decreased expression of catalase, glutathione peroxidase 4 and glutathione synthetase genes coupled with an increased expression of manganese superoxide dismutase and several other related enzymes and proteins. Thus, the severe hearing loss in these folate-deficient mice was attributable to homocysteinemia.

In view of the experiments confirming the role of MMP-9 in homocysteinemia-induced cochlear and cognitive dysfunction, we compared the auditory brainstem recordings (ABR) and cognitive abilities (new object recognition test—NORT) of $CBS^{+/-}MMP\text{-}9^{-/-}$ ($CBS^{+/-}$ mice in whom the MMP-9 gene was ablated) with those of $CBS^{+/-}$, $MMP\text{-}9^{-/-}$ and wild-type (WT) mice. It was observed that ABR and cognitive abilities significantly improved ($p = 0.0004$ for ABR, $p = 0.006$ for discrimination index of NORT as compared to $CBS^{+/-}$) by ablation of the MMP-9 gene (Bhargava et al. 2014).

In human studies, Durga et al. (2007) conducted a double-blind, randomized, placebo-controlled clinical trial on 728 older adults who had plasma homocysteine concentrations ≥13 μmol/L but who did not suffer any middle-ear dysfunction, unilateral hearing loss or pathological ear conditions not attributable to their age. It was observed that a 3-year daily supplement of 800 μg folate slowed the increase in the hearing threshold (pure tone air conduction thresholds) by 0.7 decibels ($p = 0.020$) in the lower frequencies, but did not affect the deterioration in the higher frequencies.

Gocer et al. (2009) conducted a study in 78 hearing-impaired subjects and 53 age-matched controls (no hearing impairment). The plasma homocysteine levels were significantly higher, whereas the serum concentration of vitamin B_{12} and folate was significantly lower in those with hearing impairment as compared to the controls. There was a statistically significant correlation between the pure tone audiometry and the levels of homocysteine, B_{12} and folate at 250 Hz (low frequency).

Gopinath et al. (2010) demonstrated that individuals above 50 years of age with a homocysteine >20 μmol/L had a 64% greater likelihood of hearing loss of >25 dB. This association with increased prevalence of hearing loss was also observed in individuals with low serum folate but not associated with low serum vitamin B_{12}.

At this juncture, since the inner ear is being discussed, the only study that has evaluated the effect of homocysteinemia on vertigo deserves mention. Aydin et al. (2012) studied the relation between the circulating levels of homocysteine, B_{12} and folate with peripheral vestibular dysfunction. They did not observe any correlation between these biomarkers and the three types of peripheral vestibular dysfunction—Meniere's disease, vestibular neuritis and benign vestibular positional vertigo.

Raponi et al. (2013) demonstrated that homocysteinemia may have a role in delaying recovery after acute vestibular neuritis. In their study, patients given homocysteine-lowering therapy in conjunction with specific therapy recorded a better improvement (as per the Dizziness Handicap Inventory [DHI] questionnaire) after 1 month of therapy than those given only specific therapy ($p < 0.01$).

Lacunae in Knowledge

1. Further studies need to be conducted to elucidate the optimum concentrations of various MMPs and TIMPs in the different parts of the inner ear and their correlation to homocysteinemia. Also, the role of inhibitors of MMPs and TIMPs needs to be elucidated.
2. Further studies are also necessary to establish the interplay of the B vitamins and homocysteinemia with hearing loss in other age groups.
3. There is a dearth of studies on the role of homocysteine in vestibular neuritis; this needs to be addressed.

Clinical Message

Since homocysteinemia can cause alterations in the MMP/TIMP axis in the inner ear, hearing loss of varying degrees may occur. This could be minimized by appropriate administration of the B vitamins, specifically folate.