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REVIEW

CONSIDERATIONS ON ANATOMY AND PATHOPHYSIOLOGICAL NOTIONS CONCERNING THE INNER EAR

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Abstract

Sudden hearing loss is a medical emergency requiring immediate clinical and laboratory tests, as well as an adequate and quickly established treatment. Sudden hearing loss is disabling for the patient and its permanence has implications on the patient's quality of life. According to literature data, the earliness of treatment initiation is directly correlated to therapeutic results. An individual response to therapy exists, which is due to anatomical particularities: individual vascular pattern, poor vascularity and fragility of cochlear vascularization, as well as the existence of some malformations. The knowledge of the pathophysiological mechanisms of brain ischemia led to a new paradigm in the modern therapeutic protocols for acute and aggravated stroke: the neural growth factors. Nerve growth factors are a modern and advanced therapeutic approach through multimodal effects: neuroprotector, neurotrophic and neuroregenerative effects.

Key words: cochlear vasculature, nerve growth factor, cochlear ischemia, sudden hearing loss treatment.

Abbreviations: NGF – Nerve growth factor, SHL – Sudden hearing loss, BDNF – Brain-derived

Résumé

Considérations sur l'anatomie et notions pathophysiologiques concernant l'oreille interne

La surdité brusquement installée est une urgence médicale nécessitant des investigations cliniques et paracliniques immédiates, ainsi qu'un traitement approprié et rapidement installé. L'hypoacousie brusque est invalidante pour le patient et sa permanence a des implications sur la qualité de vie de celui-ci. Conformément aux données de la littérature, la précocité du début du traitement est directement corrélée aux résultats thérapeutiques. La réponse à la thérapie est individuelle en raison des particularités anatomiques: le terrain vasculaire individuel, la vascularité pauci-immune et la fragilité de la vascularité cochléaire, ainsi que l'existence des malformations. La connaissance des mécanismes physiopathologiques de l'ischémie cérébrale a conduit à un nouveau paradigme dans les protocoles thérapeutiques modernes pour les micro-accidents vasculaires cérébraux ischémiques aigus et aggravés : les facteurs de croissance nerveuse. Les facteurs de croissance nerveux représentent une approche thérapeutique moderne et prometteuse, par ses effets multimodaux,

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neurotrophic factor, AICA – anterior-inferior cerebellar artery, LTP/LDP – long-term potentiation/depression, Ang 1 – Angiopoietin 1, tPA – tissue plasminogen activator, Shh – Sonic Hedgehog, miRs – microRNAs.

parmi lesquels on mentionne: l'effet neuroprotecteur, neurotrophique et neurorégénérateur.

Mots-clefs: vascularité cochléaire, facteur de croissance nerveuse, ischémie cochléaire , traitement d'hypoacousie.

Introduction

Sudden hearing loss is a medical emergency requiring immediate clinical and laboratory tests, as well as an adequate and quickly established treatment[1]. Sudden hearing loss is disabling for the patient and its permanence has implications on the patient's quality of life. According to literature data, the earliness of treatment initiation is directly correlated to therapeutic results[2].

Sudden hearing loss treatment is one of the most controversial issue in otology literature in the past years[3]. Regarding etiology, sudden hearing loss is a cochlear vasculopathy with multiple pathological mechanisms: spasm, thrombosis, embolism, hemorrhage. This theory is sustained by the anatomy of the cochlea, as well as the frequent association with different cardiovascular diseases (arterial hypertension, atrial fibrillation, carotid atheromatosis). The changes of cerebral vasculature and the default of the cochlear vasculature can be highlighted through imaging studies like Doppler carotid and vertebral ultrasound and angio-MRI. The correct diagnosis of the etiology is very important to establish an adequate treatment[4].

Treatment of sudden hearing loss must be chosen from a variety of therapeutic solutions and should be individualized depending on the pathogenic conditions of each patient[4]. The therapeutic results depend on many factors such as the time until presentation to medical exam, the degree of hearing loss, the presence of other comorbidities. An individual response to therapy exists, which is due to anatomical particularities. There is mild hearing loss rebellious to treatment and severe hearing loss that answers spectacular to medical treatment. The evolution of each case depends on individual vascular pattern, poor vascularity and fragility of cochlear vascularization, as well as the existence of some malformations. The fundamental and comparative studies regarding embryology, anatomy and physiology of the cochlea and cochlear vestibular nerve still remain full of unknown aspects.

The anatomical studies showed that inner ear's vascularity is composed of arteries and veins, while the lymphatic vascularity is still unknown. The inner ear's vascularity is generally separated from the one irrigating the middle ear and the bony labyrinth. However, in several cases, it was observed at the level of the inner ear canal the presence of a cerebellar anse disposed between nerves VII-VIII and called *arcuate artery* (Characon)[5]. It is the only anastomosis between the inner and middle ear vascularization and explains the relationship between the tubo-tympanic diseases and the cochlear-vestibular system. This arcuate artery arises from the middle cerebellar artery, after exceeds the posterior edge of the acoustic-facial package, at several millimeters distance from the labyrinthine artery, and which penetrates into the petro-mastoid canal where it branches on the internal wall of the mastoid antrum[5].

Arterial vasculature of inner ear

Arterial vasculature of the membranous labyrinth originates from the vessels situated within the cranial cavity, being ensured through the **labyrinthine artery (internal auditory artery)**, which often is a branch of the *anterior-inferior cerebellar artery (AICA)*. The anterior-inferior cerebellar artery is a *branch of the basilar artery* (basilar trunk), issued from the union of the two vertebral arteries, which are branches of the subclavian artery[5].

According to Guerrier, in 17.5 % of cases, the labyrinthine artery may be detached from the basilar artery or more rarely, from the vertebral artery. The anterior-inferior cerebellar artery may have the following relationships with the acoustic-facial pedicle, as mentioned by Guerrier:

- **anterior** – the most frequently – the common trunk of the middle cerebellar artery and labyrinthine artery is divided at large distance from the inner ear canal, the recurrent branches arising from the common trunk or from the middle cerebellar artery itself;
- **median** – less frequently – the common trunk is divided in the vicinity of the facial nerve, into two branches: the middle cerebellar artery and the cerebellar-labyrinthine artery;
- **posterior** – the common trunk is very short and immediately bifurcates, after crossing the external oculomotor nerve, in the middle cerebellar artery, which slides back, and the cerebellar-labyrinthine artery; the cerebellar-labyrinthine artery will divide

in the internal auditory artery and two recurrent cerebellar branches, which will form two storeyed anses advance-back, passing one over and the other beneath the nerve VIII. From the anterior recurrent branch arises the internal auditory artery.

The origin of the auditory artery can be variable, according to Mazzoni (1969)[6]:

- In 80% of cases it is a main branch of the anterior-inferior cerebellar artery.
- In 17% of cases it is a branch of the basilar artery.
- in 3% of cases it is a branch of the vertebral artery.

Localization of the labyrinthine artery in the region of inner ear canal also presents a high individual variability, as demonstrated by Mazzoni in a study made on 100 human specimens, as follows[6]:

- 40% of cases within inner ear canal;
- 27% of cases at the level of the internal acoustic meatus;
- 33% of cases in the cerebellopontine angle.

The arterial irrigation of the membranous labyrinth is ensured by one or two vessels not exceeding 200 μ in diameter, as follows[6]:

- *mono-arterial system*, where a unique labyrinthine artery exists, and which divides into **common cochlear artery** and **anterior vestibular artery**;
- *bi-arterial system*, where an inferior labyrinthine artery exists, situated on the inferior face of the cochlear nerve and which will be **the vestibulo-cochlear artery** and a superior labyrinthine artery, with a path similar to the one from the mono-arterial systems. In the mono-arterial system a supplementary artery exists, which irrigates the inner ear canal elements, without penetrating the labyrinth and which is situated beneath the cochlear nerve, having a path similar to the one of the inferior labyrinthine artery from the bi-arterial system. This mono- and bi-arterial arrangement is almost the same as frequency, and in some subjects the arterial system type may vary from one ear to the other. According to Fish, the arteries for the vestibule are bigger than the ones directed towards the cochlea, which explains the more frequent pathological damage of the cochlea.

The labyrinthine artery from the mono-arterial system, is divided into[6]:

- *Anterior vestibular artery*;
- *Common cochlear artery* that branches into:
  - *Main Cochlear artery* (which may be replaced by the cochlear branch of the vestibular-cochlear artery)
  - *Vestibular-cochlear artery* divides in:
    - *Posterior vestibular artery*
    - *Cochlear branch*.

A characteristic of these arteries is the reduced thickness of the muscular wall as compared to others vessels, which makes them very fragile, so that they can be damaged at the smallest injury[6].

The complete model of cochlea vascularization incited numerous discussions, some of the schemes widely accepted in the scientific literature is the one presented by Hawkins (1968) as follows[6,7]:

- the main cochlear artery vascularizes ¾ of the cochlea, including the modiolus;
- the cochlear branch irrigates ¼ from the basal trunk of the cochlea and adjacent modiolus;
- the anterior vestibular artery irrigates the utricle's macula, a small part of the saccule's macula, the crista and membranous portions of the superior and lateral semi-circular canals, the upper face of utricle and saccule;
- the posterior vestibular artery irrigates the macula of saccule, the crista and membranous portion of semi-circular posterior canal, the lower face of utricle and saccule.

The vascularization of cochlea is ensured by the main cochlear artery and by the cochlear branch of the vestibular cochlear artery. At the cochlea level, the vessels and nerves present a special distribution, of spiral type, proved by a radial section, performed parallel to the middle of modiolus axis[7,8].

Spiral modiolus vascularization of cochlea (according to Anson and Donaldson)

The main cochlear artery or the spiral modiolar artery, penetrates within the central canal of the modiolus, where it anastomoses with the cochlear branch of the vestibule-cochlear artery on the inner edge of the spiral lamina and then is distributed from bottom to top, being located before the spiral ganglion and having a spiral trajectory. Several primary and secondary arteries emerge from it and they immediately twist away.

The vascularization of cochlea is of *parietal* type, as following[8]:

- within the (inner) modiolar wall, towards the spiral lamina, is situated the *modiolar spiral artery* from which are detached the inner radial arterioles, which vascularize the spiral ganglion, the limbus, the tympanic edge of the osseous spiral lamina and the basilar membranes;
- within the external wall of the cochlear canal are situated the *external radial arterioles*, which form two independent vascular networks:
  - **stria vascularis**, a network rich in capillaries, forming a closed polygonal circle;
  - **vessels of spiral prominence**, located parallel to and below the stria vascularis.

The vessels of the external wall and those of the inner wall do not present between them any

anastomoses, and neither between the stria vascularis and the spiral prominence[8].

The radial arterioles are tertiary or quaternary branches forming arcades near the edge of each tour, on the tympanic lip, before the basilar membrane where they are situated, beneath the Corti canal. When the radial arterioles reach the marginal vessels, they return at right angle forming a „T" or building arcades. The radial arterioles are forming two arcades: one that irrigates the external wall structures – *the external radial arterioles*, and one irrigating the internal wall structures of the cochlea – *the inner radial arterioles*[9].

The external radial arterioles form an arcade above the scala vestibuli until the interscalar septum and, after supplying the vessels of the scala vestibuli's walls, enter into the anterior region of the spiral ligament. These vessels divide in order to form the following capillary networks[9]:

- The spiral vessels up to the spiral ligament, in the area where the ligament face of vestibular scale approaches the extension of Reissner membrane (the vessels of the vestibular scale, the vessels of Reissner membrane).
- The capillary network of stria vascularis, the vessels of spiral prominence.
- The vessels located up to the spiral ligament, on the tympanic scale face at the level of basilar crest, which serve for collecting the venules and are morphologically identic to capillaries vessels.

The capillaries vessels of stria vascularis continue the spiral direction, are interconnected and located perpendicular to the radial arterioles and collector venules, giving the appearance of a border network. These vessels are quite straight and parallel[9].

Within vestibular scale, where the vascularization is poorer, one or two thin spiral capillary vessels have been highlighted, located at the origin of vestibular membrane. In the medium scale, however, a network exists, as well as *the vessels of spiral* prominence. Both are irrigated by the external radial arterioles, but no anastomoses exist between them.

The inner radial arterioles pass very close to the basis up to the modiolus, enter within the vestibular lamina of the osseous spiral lamina, supplying the *vessels of limbus and marginal vessels* and give rise to branches for the spiral ganglion[9].

The marginal vessels form two groups of independent arcades which function together as arterial and venous canals; a group forms the vessels of basilar membrane and the other the vessels of tympanic edge of the spiral lamina.

There is a series of **embryogenetic and anatomical aspects** explaining the cochlea's increased susceptibility to ischemia:

- Cochlea is a *neo-structure* appearing in terrestrial life, and presenting a *pauci-vasculature* as compared to the posterior labyrinth, which is a paleo-structure and has bulkier vessels.
- Cochlea's vascularization is of parietal type (does not penetrate into the labyrinth) either of terminal type (non-existence of anastomoses between stria vascularis and the spiral prominence and neither between the internal and external wall vessels of cochlea).
- Cochlea presents multiple vascularization variants; the most common are the mono- or bi-arterial types.
- There is a variability of individual vascularization of the inner ear, as well as the variability between the two ears at the same patient, which may explain impaired unilateral sudden hearing loss.
- From phylogenetic point of view, the cochlear nerve is also new and therefore presents a poorer vascularization than the one for vestibular or facial nerves from inner ear canal. That's why it is the most susceptible to hypoxia, in case of extrinsic compression of the acoustic-facial package.
- Cochlea's vessels are very fragile, due to the reduced thickness of muscular wall.
- The apical part of the cochlea is characterized by a marked simplification of vascularization.
- Vestibular membrane, tectorial membrane and pectinate zone of basilar membrane are avascular.

Inner ear pathophysiology

The progresses of the molecular biology field continue to be extremely fast. Usually, for a normal mature nervous system, the neural circuits suffer adaptation modifications. In the case of a neural cell, the old synapses may regress (until their complete disappearance), with simultaneous forming of new branches (new neuritis) which will establish new synapses. These modifications of neuronal and synaptic architecture prove the high adaptation plasticity of the nervous system to the environmental conditions. Nowadays, it is considered that two major classes of intracellular factors (signals) exist, which adjust the neural development and adaptation: the growth factors (neural growth factor, fibroblast growth factor, ciliary neurotrophic factor etc.) and neurotransmitter factors (dopamine, serotonin, acetylcholine, glutamate)[10].

The equilibrium loss between the two systems of factors triggers pathological conditions. Amongst them, an important place is occupied by the degenerative disorders of the nervous system, being characterized by neuronal degeneration (neuronal death) in certain cerebral territories[11].

Generally, it can be considered that all auditory pathologies are a result of cellular homeostasis alteration. Under the impact of genetic mutations, but also of environmental aggressions, the cells must adapt to new changes. Sometimes, they are „overwhelmed" by these changes and cannot maintain their functions and anatomic integrity. The importance of maintaining the internal environment constant was observed and described many years before by Claude Bernard (1878), but since 1929 Walter Cannon proposed the term of „homeostasis" which is used also nowadays to define the cellular equilibrium condition[11]. Each cell has a multitude of mechanisms by which it tries to maintain its homeostasis: barrier membranes, transporting systems and paths of cellular adjustment. If these mechanisms of cellular protection are defeated, then the cell begins to die. Even by its death, the cell tries to protect the other cells, preferring the cellular apoptosis. Cellular apoptosis is a programmed death, an ordered disassembly of the cell, when cell wastes are internalized, and not externally eliminated, an active process requiring energy. Necrosis is the cellular death that had no time for being programmed[11]. The same phenomenon occurs also in the case of cochlear sensorial cells. At the moment, when their internal environment is imbalanced either by normal physiological imbalances occurring due to aging, either by the aggressions that we bring, either by the working conditions implying exposure to noise, either by the rhythm of life one lives and the environment where one chooses to live, the sensorial cells from Corti organ die by cellular apoptosis or necrosis.

The studies in this field showed that when hearing losses are of 40 dB and more, then the injuries occur to both cell types (external and internal sensorial cells)[12].

The role of cochlear vascular system in local degradation due to ischemia is still widely studied and far from being discovered. In the conditions of homeostasis, the cochlear blood flow is controlled by a multitude of factors[13]: systemic variations, influence of sympathetic nervous system on the cochlear vascularization, local self-regulation. Long time ago it was believed that the cochlear blood flow is in accordance with systemic blood flow[13]. In the past years it was proved that, although obviously the cochlear blood flow is influenced by the total blood flow, cochlea has its own mechanisms for regulating the blood quantity reaching to it[14]. The influence of somatic nervous system on the cochlear blood flow is due to a strong intervention starting at the level of the stellate ganglion[15], but also at the level of ipsilateral innervations from the superior cervical ganglion[16].

The cochlear blood supply is very sensitive to intrinsic factors, like carbon dioxide content of the blood flow reaching the cochlear level, but a larger series of factors are considered being implied in the cochlear self-regulation among which also nitric oxide, prostaglandins or tropomyosin[17].

The biochemical mechanisms of cerebral ischemia are extremely complex and include: necrosis (cellular death), post-reperfusion oxidative stress, „sludge" phenomenon, „no reflow" phenomenon[18]. (Figure 1A).

The ischemic loss of the brain tissue is a direct consequence of the impossibility of normal metabolic changes (in particular oxygen and glucose supply from the vessels to the brain parenchyma), due to the loss of the integrity of brain microcirculation[19]. The disruption of the microcirculation depends on the endothelial dysfunction stage, the presence of previous vascular risk factors, the development of collateral circulation, the time duration since the initial occlusion of the artery[19]. These events at the level of the microcirculation are the key-elements which allow or not the reperfusion of the brain tissue in

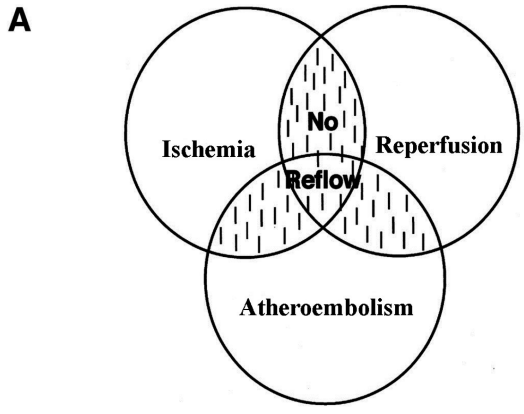

Figure 1A. No reflow is a process that starts during the ischemic period and then increases during reperfusion.

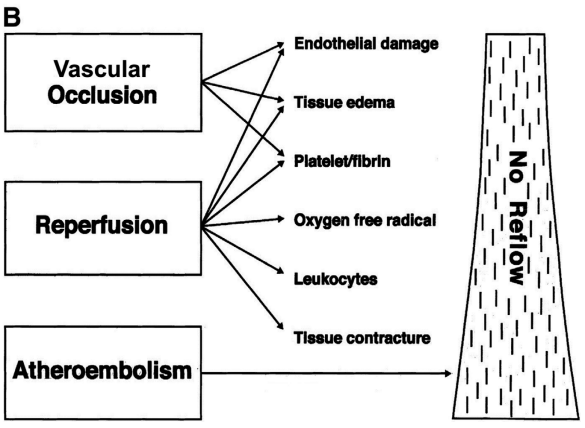

Figure 1B. Various mechanisms are implicated in the genesis of the no-reflow phenomenon.

the ischemic area, even if the treatment is initiated quickly. Understanding the role of the brain microcirculation during the acute ischemia is essential to understand the 'no-reflow' phenomenon[18,19] (Figure 1B):

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin within the brain. It regulates neurovascular functions such as neural and vascular plasticity, angiogenesis, neurogenesis and neuroinflammation. Low circulating BDNF levels were found to be associated with poorer memory performance, as well as with the occurrence of depression and stress disorder in patients with sudden hearing loss[20].

In addition, BDNF gene polymorphisms were shown to influence plasticity in the prefrontal cortex, preservation of general cognitive functioning, delayed alteration of memory processing, memory and processing speed, long-term potentiation/depression (LTP, LDP), recovery of executive functioning, and the response of depression to treatment after ischemic events[20]. Therefore, strategies aimed at enhancing endogenous BDNF seem to represent an effective option for improving neurocognitive deficits and probably auditory recovery after SHL[21].

Exogenous nerve growth factor has potent restorative therapeutic effects for the treatments of nervous ischemia. Michael Chopp, an American neuroscientist, reviewed and provided new insight into the multiple mechanisms of action of exogenous nerve growth factor. He analyzed data of double blind preclinical studies, performed under rigorous clinical trial conditions for the treatment of stroke[22]. The results showed that exogenous nerve growth factor evokes expression of Angiopoietin 1 (Ang1), which promotes blood brain barrier integrity, is anti-inflammatory and mediates axonal outgrowth [22]. Exogenous nerve growth factor also up regulates the expression of the developmental morphogen Sonic Hedgehog (Shh). Shh stimulates cellular expression of tissue plasminogen activator (tPA), which acts as both an endogenous thrombolytic agent and plays a pivotal role in mediating neurite outgrowth and neurological recovery[22]. In addition, Michael Chopp provided novel insight into how exogenous nerve growth factor stimulates specific sets of microRNAs (miRs). miRs are small non-coding RNAs which can simultaneously post-transcriptionally regulate the translation of many genes. Shh acts to up regulate cellular expression of the miR-17-92 cluster. This cluster of miRs has potent anti-inflammatory effects, as well as promotes axonal outgrowth[22].

Thus, all of these mechanisms demonstrate that exogenous nerve growth factor has multifactorial neurovascular remodeling effects on tissue which drives neurological recovery.

Conclusions

Sudden hearing loss remains an important issue in the otology literature, from the point of view of etiology and treatment. An individual response to therapy exists, which is due to anatomical particularities: individual vascular pattern, poor vascularity and fragility of cochlear vascularization. The knowledge of pathophysiological mechanisms of brain ischemia led to a new paradigm in the modern therapeutic protocols for acute and aggravated stroke: the neural growth factors. Nerve growth factors are a modern and advanced therapeutic approach through multimodal effects: neuroprotector, neurotrophic and neuroregenerative effect. The increase of endogenous BDNF levels induced by exogenous nerve growth factor might account for improving cochlear ischemic effects (tinnitus, vertigo, dizziness) and probably auditory recovery. However, large short-term controlled trials and long-term efficacy and prevention studies with peptidergic drugs are still needed.

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