

# The auditory pathway: Levels of integration of information and principal neurotransmitters

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## Abstract

*This paper addresses anatomical, physiological and neurochemical aspects of the central auditory pathway (CAP), from the inner ear, the brainstem and the thalamus to the temporal auditory cortex AC). The characteristics of the spiral ganglion of Corti (SGC), the auditory nerve (AN), the cochlear nuclei (CN), the superior olivary complex (SOC), the lateral lemniscus (LL), the inferior colliculus (IC), the medial geniculate body and the AC, including the auditory efferent pathway, are given. We describe how electrical impulses travel through the axons, which allow for ions to enter in neurons and release vesicles with neurotransmitters (NT) into the synaptic space. NTs modify the functioning of cells by binding to specific receptors in the next neuron; The NT-receptor bond causes the entry of ions through Gap sites, which generates a postsynaptic potential that spreads across the entire CAP. Furthermore, the effects of the NTs are not restricted to transmission, but, since they are trophic agents, they promote the formation of new neural networks. The anatomy, physiology, neurochemical aspects and the different types of synapses of the CAP are not yet fully understood to comprehend its organization, but they continue under investigation due to their relevance for the treatment of different central auditory disorders. (Gac Med Mex. 2014;150:447-56)*

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## Introduction

The CAP, from the cochlea to the primary AC at the temporal lobe, is sequential and complex, reflecting different levels of auditory information analysis. It comprises different parallel pathways, involving several neurons and NTs, which form a series of monoaural and binaural processing circuits.

The CAP starts at the primary neurons of the SGC, which project their axonic prolongations through the AN towards the CNs located at the posterior-inferior part of the medulla oblongata in the brainstem. From there, the information preferentially crosses the middle line to approach the SOC at the anterior-inferior part of the annular protuberance; this is the first relay station receiving information from both ears (binaural) and, therefore, it is involved in spatial localization of sound. Subsequently, other fibers reach the LL and the IC,

directly in a posterior location at the midbrain. Auditory information continues its way to the medial geniculate nuclei (MGN) at the thalamus and, finally, it arrives to the primary AC at the temporal lobe (Fig. 1). Additionally, the EAP is also known to flow in opposite direction to the afferent CAP. There is more information available on the EAP that goes from the SOC to the cochlea<sup>1,2</sup>.

## Auditory nerve

The innervation of inner ear hair cells consists of neuronal dendritic terminals, whose cell bodies form the SGC. The exact number of cochlear cells is unknown, but in the cochlea of the child it is deemed to be ~ 33,500 neurons<sup>3</sup>, and Spoendlin et al. established even up to 41,000 neurons in myelinated nerve fibers from normal hearing individuals<sup>4</sup>. The characteristics and neuron numbers of the auditory pathway (AP) vary according to the species; mammals have different types of cochlear neurons: type I are large and bipolar and connect exclusively to inner hair cells in the organ

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whereas the ventral CN has mainly large cells. In turn, the subdivisions are formed by different types of cells; the main four are the spherical and globular bushy cells, octopus cells and multipolar stellate cells. In the dorsal CN there are five types of cells: fusiform, radiated, fan-shaped, cartwheel and small stellate cells. Dorsal CN cells project their axons into the dorsal acoustic stria, where they cross the medial division of the LL (Monakow area). Other axons ascend from the CNs and finally terminate on the LL and IC dorsal nuclei.

The ventral CN cells bodies project their axons to the homolateral accessory olive and to medial dendrites of the contralateral accessory olive cells in a higher percentage, which represents the basis of the most important crossover of AP fibers. There is a spatial projection of the anterior ventral CN towards the SOC and from there they approach the LL and ascend to the IC<sup>7</sup>.

### **Superior olivary complex**

This nucleus seems ideally built for the processing task in the binaural localization of sound, by analyzing features such as intensity differences and interaural time. It is comprised by three major nuclei: the lateral and medial superior olivary nuclei and the medial trapezoid body. In turn, these nuclei are surrounded by several diffuse small nuclei, collectively known as dorsal periolivary nuclei, which comprise heterogeneous populations of neurons with high structural, physiological and neurochemical diversity, as well as complex neural connectivity models and ascending and descending fibers. The medial superior olive projects its fibers bilaterally in the medial divisions of the LL to terminate on the LL dorsal nucleus and the IC. The lateral superior olive projects homolaterally to the lateral division of the LL to terminate on the dorsal nucleus of the LL. Some fibers continue and terminate on the IC. No SOC neuron goes further than the IC<sup>8</sup>. It is worth mentioning that, in multisensory stimulation (visual and auditory), the auditory system is responsible for the perception in time through the capture of time differences, whereas the visual system is responsible for spatially organized information.

### **Lateral lemniscus**

The LL begins caudally, where the axons of the contralateral CNs and ipsilateral to the SOC intermingle to form a single tract. The CAP ascends dorsostrally across the lateral pontine tegmentum and terminates on the IC. The LL contains ascendent and descendent

axons of the AP; intermingled with them are the neurons that comprise these nuclei. The ascendent LL auditory fibers include those originating in the CNs and the SOC, as well as those originating within the LL's own nucleus; many of these fibers terminate on the IC. A substantial number of these fibers originating in the LL cross the IC, to terminate on the superior colliculus, whereas other few reach the MGN. The LL is comprised by three morphologically different large nuclei, but joined together in such a way that they form a chain that acts as a bridge between the SOC and the IC. These nuclei are named after their position: ventral, medial and dorsal. They form multi-synaptic pathways parallel to other ascendent pathways<sup>9</sup>.

The ventral LL is comprised by two areas that appear in several mammal species (columnar area and multipolar area); it receives contralateral projections from the CN and projects ipsilaterally to the central nuclei of the IC, and a large majority of minor projections cross the brainstem up to the contralateral IC<sup>10</sup>.

The medial LL is a transition zone between the ventral and dorsal LL. Neurons in this nuclei project ipsilaterally to the IC and probably to the medial geniculate body (MGB).

The dorsal LL nucleus is comprised by a large group of neurons, included among the ventral LL fibers. It is formed by different types of neurons preferentially oriented in a horizontal plane. This nucleus projects mainly to the IC and bilaterally to the superior colliculus and, to a lesser extent, to the medial and dorsal division of the MGB. The projections of this structure to the IC are tonotopic. Additionally, it projects to deep layers of the superior colliculus, providing auditory inputs to this structure; thus, neurons of the superior colliculus region not only respond to visual and somatosensory stimuli, but to auditory stimuli as well.

### **Inferior colliculus**

The IC is found in the midbrain, where the AP, previously diverging from the CNs up to the multiple ascending tracts, now converges again. Although the IC has direct connections of second order ipsilateral and contralateral fibers coming from the CNs, a large number of afferent fibers make synapses at the SOC and the LL. A few LL fibers avoid the IC terminating directly on the MGB. However, the IC can be considered a mandatory synapsis relay station for the vast majority of afferent auditory pathways that favor a summation of the auditory processing by the brainstem. The IC is comprised by different subdivisions: a large nucleus

divided into a non-laminated dorsomedial division and a laminated ventrolateral portion; these nuclei are covered by a pericentral nucleus. The IC central nucleus receives efferent auditory projections; but auditory projections to the cortex and paracentral nuclei are structurally thick and also receive cortical somatosensory descending projections. The laminar organization of the central nucleus observed in anatomical studies suggests a functional organization as well<sup>11</sup>.

### Medial geniculate nucleus

A thalamic auditory relay towards the cerebral cortex, this structure is divided in dorsal, ventral and medial divisions. The distant projections of the IC go mainly to the MGN, and from there, to the superior colliculus and other lower neural centers. There are no neurons projecting from the CNs or the SOC to the MGN, which is why the existing neuronal terminals are originated in the IC and/or the ventral and dorsal nuclei of the LL.

As previously mentioned, there is crossing between the LL dorsal nucleus and the IC. Ascending neurons are connected with the reticular formation and non-ascending neurons are directed towards the MGN. The main part of the MGN inferior nucleus is comprised by small neuronal bodies that project to the primary AC. There is a spatial arrangement of the neuronal projections to the AC (tonotopy); this way, the anterior portion of the main part of the MGN terminates on the rostral portion of the primary AC, and the posterior portion of this structure, on the caudal part of the AC<sup>12</sup>.

### Auditory cortex

In humans, it is located in the superior temporal gyrus and deeply buried in the lateral sulcus. It is divided in primary AC and secondary AC, as well as several association areas (auditory fields), including the anterior, posterior, ventroposterior and cortical posterior ectosylvian fields.

The rostral portion of the primary AC is formed by neurons that respond to high frequencies, whereas neurons comprising the caudal portion respond to low frequencies. These areas receive projections essentially from the rostral portion of the main part of the MGN. However, this arrangement is not simple, since recent anatomical and physiological studies show highly complex neural networks, and no arrangement has been proven to be as ordered as the one coming from the CNs to the MGN<sup>13</sup>.

### Efferent auditory pathway

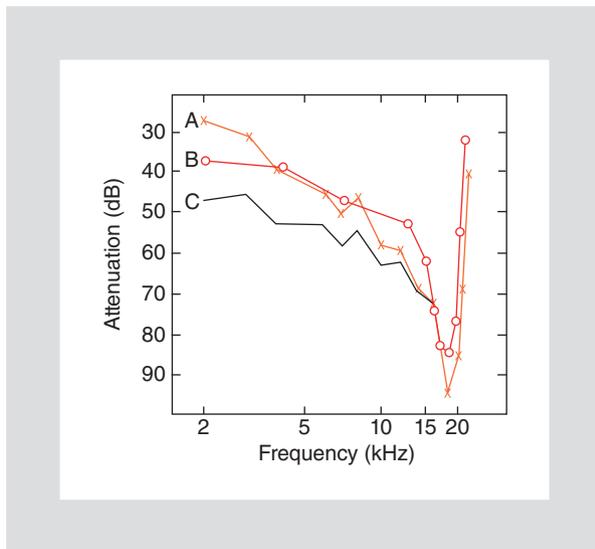
Although the ascending (afferent) AP is better known, the ear has a descending (efferent) pathway as well, with neurons running parallel to the former. Even though little is known about this pathway, it is deemed to regulate the AC function with the lower auditory centers and Corti's organ.

The efferent innervation of the cochlea by cells located at the SOC was first described by Grant-Rasmussen in 1946<sup>14</sup>. This pathway is considered to be a feedback control for auditory receptors. Scientists have been able to provide evidence that electrical stimulation of the AC induces a neural response at the SOC level, which has two neuron systems linked to this efferent pathway: the lateral and the medial nucleus. Neurons of the lateral SOC contact afferent fibers in the region of inner hair cells, whereas the terminal axons of the medial SOC make synapses with external hair cells. The function of the lateral system is unknown, but its connections suggest an axon-axon direct modulatory effect on the AN fibers, which is why the medial system of the SOC suppresses the AN fibers indirectly through a mechanism involving the external hair cells in a such a way as to modulate their movement.

### Physiology of the auditory pathway

The resolution of auditory frequencies is the ability of the hair cells and neurons of the CAP to selectively respond to the frequency of an acoustic stimulus. It is an auditory capability that is fundamental to the reception of all sounds, including language.

The representation of the sensory stimulus entails a complex analysis of the neural responses through a tonotopically-organized arrangement of the auditory neurons from the CAP. The signal processing is performed by transforming the representation of the stimuli at the entrance of the neuronal bodies and their representation through organized axons at the exit of this group of cells. This capability is an important part of a physiological process of the CAP and includes the functioning of the peripheral portion of the ear up to the AP of the brainstem and the primary AC. The different nuclei of the brainstem have been observed to have a potential for the generation of "distant fields" responses when a sound stimulus is applied, which is the basis of the brainstem auditory evoked potentials (BAEP) register and the auditory steady-state responses<sup>15,16</sup>.



**Figure 2.** Syntonization curves of the three AN fibers. Their characteristic shape can be observed, with a pronounced valley at the lowest response intensity, which corresponds to the “characteristic frequency” for each fiber.

There are three ways to preserve the analysis of frequency selectivity that is observed in the AN. First, through the excitatory connections between the AN fibers and postsynaptic cells of the CNs, as it occurs in the anterior ventral CN, densely populated by cells able to preserve much of the information contained in the stimuli of the AN. Second, by the convergence of several AN fibers on the CNs cells, which can accelerate the time of information processing. Finally, by inhibitory fibers, which can also sharpen spectral selectivity; these fibers have been observed to be present in the entire surface of the CNs, where general inhibitory mechanisms can modulate unitary activity. The frequency selectivity is usually given by a quality factor known as Q10 or characteristic frequency across the bandwidth of a stimulus above a 10 dB threshold<sup>17</sup>.

“Syntonization curves” have been determined for hair cells, the AN and several cells of the CNs, where responses with a clear spectral selectivity are observed, with high-frequency ranges above 2,000 dB/octave, much better than the response observed in the AN fibers (150-500 dB/octave) (Fig. 2). The difference between these responses is largely due to a spontaneous suppression of neural activity by tone, to the presence of highly selective suppression or “lateral inhibition” mechanisms, similar to that what happens in the visual system. Therefore, inhibition of lateral bands improves the selectivity for characteristic frequencies of the AN fibers over time.

Other CAP mechanism is the ability to temporarily codify specific stimuli. The most common involves the synchronization coefficient, which is a measure of the “phase closure” that ranges from 0 (at random) to 1 (perfect closure). The phase closure behavior of the CNs cells relates to their ability to codify signals as complex as speech; selective cell groups codify the tone of voice, since they contain amplitude and modulated frequency components that are differentially codified across the CAP<sup>18</sup>.

The sound spectrum represented through the tonotopic arrangement of the NA fibers displays two analysis variables: range and temporality. In the CNs, the AN generates multiple selective representations; for example, range and temporality are observed to have separate representations in populations of bushy and stellate cells, respectively.

Studies with microelectrodes have shown that there are three tonotopically organized regions in the CNs, corresponding to the three anatomical divisions (anteroventral, posteroventral and dorsal). Two types of cells, globular and spherical bushy cells, are the main generators of the NCs potentials at the entrances of the medial and lateral SOC. Furthermore, other types of neurons are present, such as the stellar, octopus, multipolar, fusiform and granule cells. Each cell possesses a different dendritic and axonal morphology, and responds to different patterns of stimuli, inhibitory or excitatory, whose separate computed results are carried out in parallel in the CNs. It is probable that in the addition of the responses by the most important cells of each CN region, small neurons will be found to be in synchrony, corresponding mainly to interneurons such as the granule cells, located at the dorsal CNs, which send axons to the fusiform cells. Thus, flows of information from numerous internuclear tracts pathways have been observed. As a consequence, a physiological diversity in the responses by the CNs is observed, including spectral selectivity responses, as well as in response time and in the response by the field, among others.

The SOC plays a decisive role in binaural processing, since these nuclei have binaural entrances and codify interaural differences in terms of acoustic stimulus intensity and arrival time. Medial and lateral SOC neurons differential response depends on the integration of excitatory and inhibitory synaptic inputs, which carry information on that what happens in the cochlea. The stimuli provided to the medial and lateral SOC by the CNs are transmitted by two pathways: spheric (excitatory) and globular (inhibitory) bushy

cells. Subsequently, they are relayed by the periolivary nucleus neurons, specifically in the medial and lateral nuclei of the trapezoid body.

Originally, the SOC was thought to be an acoustic reflector center that provided afferent stimuli to movement motor centers of the head and eyes. Recent studies indicate that this nucleus is also involved with the control of the acoustic information transmission efferent system of the cochlea and the processing of the acoustic signal. The SOC contains neurons that provide efferences to the CNs and to the cochlea itself. Small bundles originating in medial areas of the SOC, which cross the superior middle line and connect the vestibular nerve, have been described; these bundles are comprised by periolivary neurons axons surrounding the main nuclei of the SOC and are known as olivocochlear fibers (OCF), return fibers of bilateral projections to the cochlea. On the other hand, the SOC receives contralateral and ipsilateral – to a lesser extent – inputs from the CNs, which supports this structure as being the most important binaural processor.

The advantages of this auditory binaural processing are the detection and localization of the sound source in space, as well as the detection and discrimination of noisy signals. If we know that each ear is located in a median plane, perpendicular to the sagittal middle line, a sound generated by a direct source opposing the ear by 90° (with respect to the azimuth) must travel around the head until it reaches the opposite ear. Therefore, the beginning of the acoustic signal spreads out to the radius of each ear before reaching the opposite ear with interauricular time differences, which are determined by the distance between the ears and the speed of sound. The interaural phase difference also occurs as a result of the distance difference the acoustic signal travels with from the point of emission until it reaches both ears. When the acoustic signal is complex in form, as the modulated amplitude signal, differences in interaural level and time produce variations in time. The resulting interaural spectrum differential inputs can be used in the localization of high frequency, free fields and sound source<sup>19</sup>.

The neural processing of each one of these binaural inputs involves the comparison of the neural activities resulting from the stimulation of both ears. Numerous theoretical models have been developed to describe the binaural sound perception phenomenon at the SOC. Two basic inputs, used in the binaural localization of sound, have been identified: the interaural phase difference (IPD) for low frequency waves, and the interaural level difference (ILD) for high frequency

waves. Other proposal is the “duplex” theory of sound localization, which describes two separate systems operating in binaural audition: the low frequency systems, which use the resulting IPD when the signal has a longer wavelength than the distance between both ears, and the high frequency systems, which operate with the ILD created by “acoustic shadow” effects of the head and the pinna.

The sound localization models initially proposed converge primarily with the usefulness of specific characteristics of the IPD neural processing. This theoretical interaction model in the CNS is dependent on neural discharges as related to the stimulus, the time of which is critical in the IPD process.

According to this model, the IPD system receives excitatory stimuli from both ears, which produce a neural discharge of the system only when the input stimuli are concurrent with the time of arrival to this system. A basic assumption of these models is that the timing of the stimuli in the IPD central model is related with the periodicity or frequency of the stimuli. This means that the input neurons must generate discharges that are synchronized to a certain phase polarity of the tonal stimuli. Thus, the IPD is represented as the time difference between both ears'-originated discharges, with the system basically being a coincidence or cross-correlation detector operating on the phase closure discharge for low frequency stimuli.

The phase closure decreases with increasing frequencies (5,000-7,000 Hz). This capability of the phase closure for high frequency waves is not associated with the tone characteristics of the frequencies. However, closure phase discharges can provide the necessary stimuli for the determination of the IPD for frequencies lower than 3,000 Hz used to localize the sound by means of binaural information.

Binaural processing of information is important not only in the localization of the source of sound, but also in the elimination of noisy signals. Binaural audition provides significant advantages in the detection of intelligent speech in a noisy environment. This binaural advantage is deemed to be the result of neural processing by binaural inputs, especially those produced by acoustic diffraction effects in reverberating environments that result in spatial separation of signals and noisy sources.

In spite of the importance of the LL nuclei in auditory processing, these have received little attention compared to that given to other nuclear complexes comprising the CAP. Furthermore, knowledge on their synaptic organization as related to their connections with the

brainstem nuclei is still rather poor, with their functional role in hearing being only known in a limited manner. Some studies suggest that the ventral LL is involved in the codification of auditory stimuli temporary characteristics. The ventral LL nucleus may be a fundamental component in the perception of language.

Since the ventral LL receives contralateral projections from the CN, these inputs are reflected in neural responses, where the majority of neurons are influenced only by contralateral stimulation and produce very short-lasting phasic responses. The neurons responsible for such responses can carry out the processing of information to higher auditory centers, involved with the temporary analysis of auditory stimuli.

The dorsal LL is important in the codification of sound, since it is the source what specifically limits the response of neurons to interaural differences in time and intensity; many of these units are contralaterally stimulated and inhibited by similar ipsilaterally-applied stimuli.

The ICs respond to binaural signals coming from the SOC; therefore, they reflect the interactions of the SOC with this structure. The fine characteristics of this processing that favors some descriptions of the collicular cells responses on several aspects of auditory stimulation are not known. Recent studies using unitary and multiunitary neuronal registers have shown the presence of a tonotopic organization in the IC central nucleus. Deep registers observed in this same nucleus have indicated a gradual increase in the main neuronal frequencies. There is also evidence that the mapping of frequencies in the central lateral nucleus is not equal to that of the medial and central regions. This regions show fine differences in cell characteristics with regard to latencies, thresholds and sensitive modulation.

The MGNs show a tonotopic organization in the ventral segment. Low frequencies are located laterally, and the higher ones, medially. Syntonization curves range from thick to sharp. There are neuronal populations sensitive to mono- and binaural stimuli, as well as to IPD. It is possible that the language discrimination process starts in this place, since groups of MGN neurons are responsible for the analysis of the acoustic parameters of speech.

There are several routes through which the MGN cells leave in direction to the AC. The most important originates in the ventral MGN; its fibers take a sublenticular course through the capsule inside the Heschl's gyrus. Other pathway comprises auditory, visual and somatosensory fibers that go from the inferior segment of the capsule connecting to the insular and temporal

lobes. Other one is formed by the path that brings to basal nuclei such as the putamen, the caudate nucleus and the amygdala, which are visited previously to their arrival to the AC.

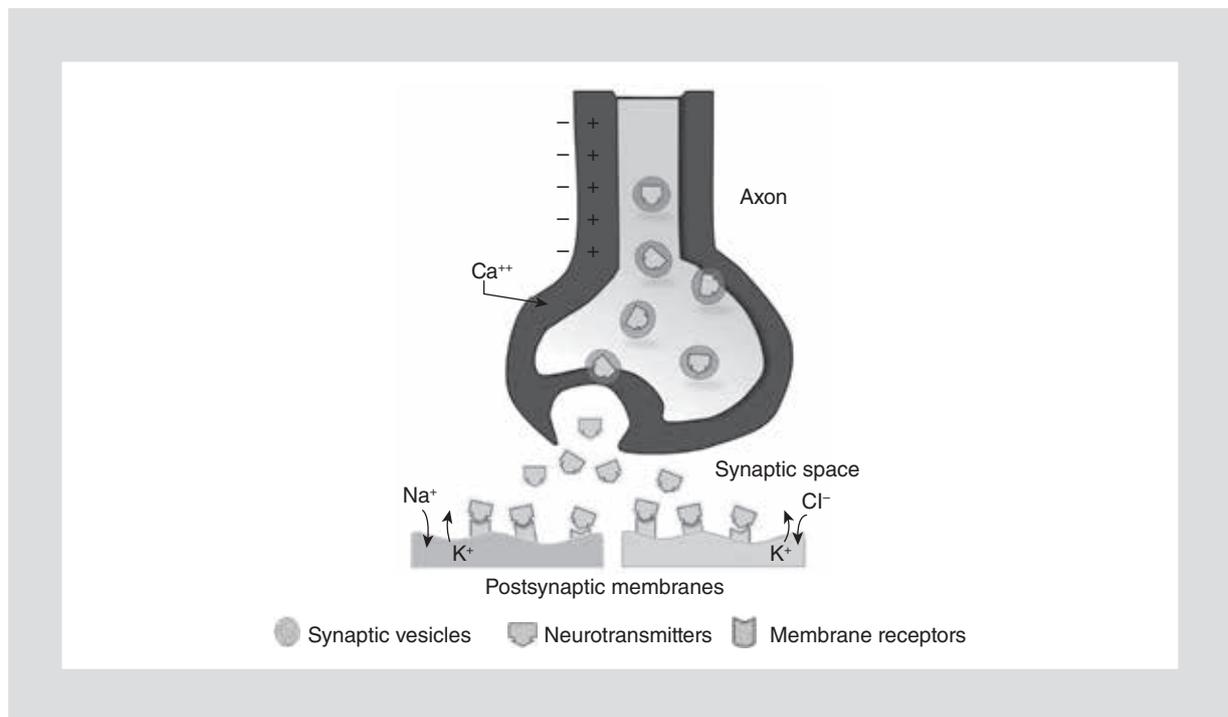
In the BAEP, the synchronized activity of the AP in the brainstem is registered. In this register, a first vertex positive wave is formed before 2 ms (at 80 dB stimulus intensity), which is known as wave I and derives from the AN. This wave is followed by a deep valley, out of which another positive wave of lesser magnitude emerges, known as wave II, which in some subjects may be absent; activity of these components originates in the CNs. Subsequently, another positive, very constant wave is formed, known as wave III, which is thought to originate from the SOC activity and is produced at 3 ms. Wave IV is small and can be absent in some subjects. Wave V is the largest and is produced around 5 ms due to synchronization of the IC neurons. Waves VI and VII have less amplitude, may be absent in normal hearing persons and represent the MGN and AC activity, respectively<sup>15</sup>. The correlation between brainstem-located lesions and disturbances of the different BAEPs' waves has been described as being very good in autopsy-confirmed disorders<sup>20</sup>, which reinforces the usefulness of the technique.

There is increasing interest in research on the sound processing characteristics across the AP and its perception for the use of cochlear implants. Physiological characteristics of the different findings on the AP nuclei at the brainstem are vital to discriminate the detection of frequency, intensity, spatial localization and timbre spectrum of each sound; they are highly relevant for people with neonatal-onset hypoacusis and with an auditory neuropathy<sup>21</sup>, and they are under study.

## Neurotransmitters

In the sensory systems, there are millions of neurons able to receive and transmit electrochemical stimuli, which form neural networks or pathways that transmit impulses from the place a stimulus (sensation) is registered and travel through an entire neural pathway until they are integrated to superior nuclei of the nervous system (perception).

Electrical stimuli depend largely on the concentration of Na<sup>+</sup> and K<sup>+</sup> ions being different in the interior and exterior of neurons (Fig. 3). The external environment is richer in Na<sup>+</sup>, and the internal, in K<sup>+</sup>. Ion carriers in the neuronal membrane exchange these ions through pores, in order to maintain an optimal balance within the cell. The interior of the axon is negative with



**Figure 3.** The electrical impulse through the axon allows for the exchange of different ions, thus releasing synaptic vesicles with neurotransmitters into the synaptic space. The neurotransmitter-receptor bond causes a positive or negative ions exchange, which generates a postsynaptic potential that spreads across an entire neuronal pathway

respect to the exterior, which generates a charge difference (resting potential). When a nervous impulse is initiated in the axon, the membrane becomes permeable to Na<sup>+</sup> ions through protein channels in an infinitesimal fraction of 1 s; consequently, the inner surface of the membrane changes from negative to positive (depolarized membrane) and becomes repolarized with the same speed. This change in ionic permeability is described as action potential, which generates the electrical stimulus that travels through a nervous pathway.

A NT is a molecule that is synthesized in neurons, which is able to modify the functioning of other cell. This chemical communication depends on the NT passing from one neuron to another through spaces known as synaptic spaces or synapses. The electrical impulses travelling from the neuronal body, through the axons, up to the synaptic space, allow for Ca<sup>++</sup> to enter in the neuron and release synaptic vesicles with NT into the synaptic space. NTs bind to specific receptors in the next neuron or cell (postsynaptic). The NT-receptor bond causes for positive (Na<sup>+</sup>, Ca<sup>++</sup>) or negative (Cl<sup>-</sup>) ions to enter through communication channels between neurons known as tight bonds or Gap sites, with their directional flow generating a

postsynaptic potential that spreads across an entire neuronal pathway<sup>22,23</sup>.

According to the actions they exert, the NTs can be excitatory, such as acetylcholine (ACh), noradrenalin, serotonin (5-HT), dopamine (DA), glutamate (Glu) and aspartate, or inhibitory, such as the gamma-aminobutyric acid (GABA), glycine, taurine and alanine. NTs are not randomly distributed in the brain, but they are located in specific groups of nervous cells. On the other hand, there are different types of receptors: cholinergic, adrenergic, dopaminergic, GABA-ergic, serotonergic, glutamatergic and opioid, among others. The NT-receptor bond must conclude immediately in order for the receptor to be able become repeatedly activated. For this, the NT is captured by the postsynaptic ending and destroyed by enzymes near the receptors (Fig. 3). There are more than 90 different NTs, but the most prominent in the OCFs are: ACh, DA, noradrenalin, 5-HT, Glu and GABA<sup>24,25</sup>.

### Acetylcholine

ACh is synthesized by ACh-transferase from acetyl-CoA and choline. ACh release is mediated by Ca<sup>++</sup>

ions, to open a cholinergic vesicle and, once inside the synaptic space, bind to its receptor in the postsynaptic membrane to exert its effect. Neurons from the cochlear efferent system communicate with sensory hair cells by releasing ACh; specific receptors of these cells (cholinergic nicotinic receptors) recognize ACh, and when they become activated, they open to allow for  $\text{Ca}^{++}$  to enter into the cell by activating changes in the resting potential of the membrane. ACh has an inhibitory function, it is released by efferent contact and originates in the OCFs<sup>26,27</sup>.

### **Dopamine**

DA is a catecholamine with both hormonal and NT functions. It is synthesized from tyrosine, which is obtained from dietary phenylalanine, and with the involvement of the tyrosine hydroxylase and DOPA-decarboxylase enzymes, which are found in dopaminergic neurons. DA exerts its functional effects by activating five metabotropic receptor subtypes, grouped in two pharmacological families: D1 (D1 and D5) and D2 (D2, D3, D4). Several CNS disorders, such as Parkinson disease, schizophrenia and drug addiction, have been associated with dopaminergic transmission abnormalities<sup>28,29</sup>.

### **Serotonin**

Serotonergic neurons are extrinsic to the auditory system, but they send projections to most auditory regions, which release 5-HT synthesized from tryptophan originating in the diet. If an increase occurs in levels of behavioral activation and specific extrinsic events, including stressing or social events, the availability of 5-HT in the AP is increased. Although the release of 5-HT is likely to be relatively diffuse, very specific effects are achieved in the auditory neural circuits through serotonergic projections and a large variety of receptor types expressed in specific subsets of auditory neurons<sup>30-32</sup>.

### **Glutamate or glutamic acid**

Glu acts at the synapsis between hair cells and afferent dendrites; the glutamatergic stimulus is needed in order to perform multiple excitatory functions. Glu is synthesized with  $\alpha$ -ketoglutarate and glutamine by the action of glutaminase and is stored in presynaptic vesicles. Its release is mediated by depolarization and by positive feedback, which allows for a released Glu

molecule, by binding to a presynaptic receptor, to induce the release of other molecules. There are two subtypes of ionotropic receptors: AMPA-GluR2/3 receptors, which are more active in the postsynaptic structure under physiological conditions, and the NMDA-NR1 receptors, which act under noisy conditions. Metabotropic receptors have been also found both in presynaptic and synaptic structures<sup>33,34</sup>.

### **Gamma-aminobutyric acid**

GABA inhibits the transmission of signals to nervous terminals; it is the main inhibitory NT both at the central and peripheral level and it is synthesized from Glu, through the Glu-decarboxylase enzyme<sup>35-37</sup>.

Synaptic signals are often electrochemical, with presynaptic depolarization by an action potential opening of  $\text{Ca}^{++}$  channels, which activate the exocytosis-mediated release of synaptic vesicles with NT, which spread and bind to postsynaptic receptors. There are receptors associated with regulated ionic channels; in response to the receptor-NT bond, a free-energy change occurs, which modifies the structure of the channel by opening it (ligand-dependent ionic channels); there are two types of opening: permeable only to cations (only a few NTs act on these receptors: ACh and Glu –and probably aspartate and ATP–, and produce rapid excitatory potentials) and permeable mainly to  $\text{Cl}^-$  (they act on GABA and glycine, and produce rapid inhibitory potentials). There are also other independent receptors, not associated with ionic channels, where the NT-receptor bond produces a cascade of enzymatic events, activated by G-proteins or second messengers such as cyclic adenosine monophosphate (cAMP) and  $\text{Ca}^{++}$ , and kinases that promote the opening of independent ionic channels. In many synapses, all types of receptors are present and respond to one or more NTs, hence the great functional diversity. Furthermore, the effects are not restricted to transmission, but serve as trophic agents that promote the formation of new neural networks and the reorganization of synapses resulting from sensory experience or lesions. Finally, the NTs are not eliminated by diffusion, enzymatic degradation or recapture within the cells<sup>38,39</sup>.

Several details on the anatomy, physiology, neurochemical aspects and various types of synapses are not yet fully understood to comprehend the organization of the CAP, but they continue being investigated due to their relevance for the treatment of several central auditory disorders.

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