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Serotonergic Innervation of the Inner Ear: Is It Involved in the General Physiological Control of the Auditory Receptor?

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Abstract: The auditory pathway of mammals is composed of two complementary ascending afferent and descending efferent independent systems. The brainstem nuclei and cochlear projections for these systems are now well-known. In addition, a highly conspicuous distribution for serotonergic fibers was recently reported. This study focused on these serotonergic fibers and their neurons of origin. We identified several different types of serotonergic brainstem neurons surrounding the superior olivary complex and around the periolivary nuclei. Even though the 5-hydroxytryptamine (5-HT) efferent cochlear innervation originates in the periolivary area of the superior olivary complex system projecting to the cochlea, it is not involved in the transduction of pure tones during auditory processing. However, recent findings, after cochlear blockade of serotonin transporters, strongly suggested that this neuroactive substance has an important turnover within the auditory receptor. The presence of a conspicuous peripheral nerve distribution together with a particular brainstem origin could define a complex role for this innervation. Therefore, 5-HT fibers projecting to the cochlea might be involved, as in other parts of the auditory pathway, in alertness, attention, control of sleep or wakefulness cycles, and state of urgency prior to the transduction processing at the auditory receptor. A lack, or reduction, of the function of these fibers could result in pathological alterations.

Key Words: auditory system; cochlear serotonin; high-performance liquid chromatography and electrochemical detection; immunocytochemistry

AFFERENT AND EFFERENT INNERVATION OF THE AUDITORY RECEPTOR

Our study focuses on the morphological structure, origin, and functional capacities of inner-ear serotonergic innervation. Comparative analysis with other cochlear innervation systems and their neurotransmitters acting on the auditory function was necessary to achieve the study's goal. Three main types of nerves have been involved in cochlear innervation: afferent, efferent, and sympathetic nerve fibers [1–3].

The afferent nerve fibers that create a synapse with sensory cells (inner [IHCs] and outer hair cells [OHCs]) are dendrites of the spiral ganglion neurons that also project on the brainstem cochlear nuclei throughout the auditory nerve (Fig. 1) [1]. Spiral ganglion neurons participate in the coding of the auditory message and are sensitive to glutamate stimulation, as was indicated by morphological [4,5] and functional studies [6–10].

Conversely, efferent fibers are mainly involved in modulation of the auditory message, even though they could also participate (through some of their neurotransmitters such as dopamine or GABA) in the protection of afferent fibers against injury [11]. Efferent nerve fibers belong to neurons of the superior olivary complex [2,11] and reach the cochlea by two main bundles: the olivocochlear lateral efferent (OLES) and medial efferent (OMES) systems. The OLES originates from neurons of the lateral superior olive (LSO), and OMES originates from neurons of the medial superior olive (MSO) and ventral nucleus of the trapezoid body [2,11]. Even though efferent systems send projections to both cochleas, the crossed fascicle seems to be more

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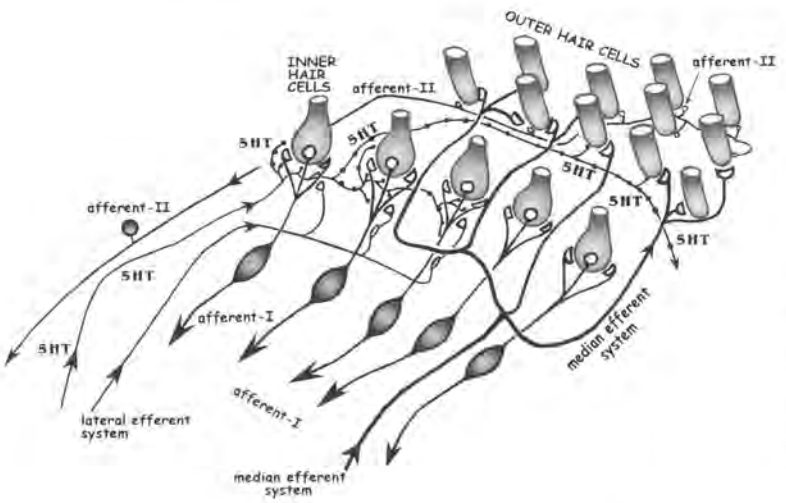

Figure 1. Scheme summarizing the distribution of afferent (type I and type II), efferent (lateral and median systems), and serotonergic (*5-HT*) fibers reaching the auditory receptor. The 5-HT fibers reach the inner spiral bundle (under the inner hair cells), then make contact on afferent type I nerve fibers and enter into Corti's tunnel, following a spiral pathway and connecting to outer hair cells.

relevant. Efferent fibers of the OLES establish axodendritic synapses and terminolateral axodendritic synapses on type I afferent nerve fibers [4,5].

NEUROTRANSMITTERS WITH A FUNCTIONAL ROLE AFFECTING THE AUDITORY RECEPTOR

In the adult mammalian cochlea, the OLES fibers contain an important variety of neurotransmitters, among them acetylcholine, γ-aminobutyric acid (GABA), and dopamine and neuropeptides [12,13]. Acetylcholine has been identified also in OMES fibers by the presence of choline acetyltransferase (ChAT) [12,14–17].

Presence and Function of GABA in the Mammalian Cochlea

The presence and distribution of GABA-containing fibers in the adult mammalian cochlea has been clearly identified [12,13,18]. A classic OLES distribution was found in synapses connecting afferent dendrites [18–21]. However, at the apical cochlear coil, a particular distribution of GABA-containing fibers reaching OHCs directly was also described [18,21]. This particular subset of GABA fibers could exhibit a functional activity clearly differentiated from that of other GABA nerve fibers.

GABA could have a very important role in the protection of afferent nerve fibers against injuries. To provide additional information on such a hypothesis, we used an experimental model of prevention of lesions induced by a glutamate agonist [22,23]. Experimental pretreatment with $GABA_A$ agonists, intraperitoneally administered, clearly indicated that $GABA_A$ receptors, without excluding the presence of G-linked $GABA_B$ receptors, are present and active on type I afferent nerve fibers [24]. These results fit well with previous data of the modulatory activity of GABA nerve fibers on the afferent system [25] and with very recent studies that concluded that $GABA_A$ receptors could play an important role in the treatment of tinnitus [26–28].

Presence and Function of Dopamine in the Mammalian Cochlea

Biochemical studies early found the presence of dopamine and its main metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid) in homogenates of whole cochleas of rat [29–31]. Dopaminergic fibers were identified as a part of the OLES fibers reaching the inner spiral bundle, under the IHCs [12,32,33].

Experimental stimulation of dopamine receptors suggested that dopamine could play an important role as a regulatory molecule of the afferent type I nerve fiber activity and cochlear potentials [34]. Acoustic white-noise stimulation resulted in the release of dopamine and the increase of dopamine cochlear turnover during acoustic stimulation, which involves dopamine receptors in auditory receptor neuromodulation [24,31,35–37]. Significant differences in dopamine turnover were observed between male and female rats. In addition, dopamine may protect type I afferent dendrites against acoustic trauma or hypoxia [38–40].

Other Neuroactive Substances in the Cochlea

Such neuropeptides as enkephalins, dynorphins, and calcitonin gene-related peptide have been identified also in the OLES fibers within the inner spiral and tunnel bundles [12]. Calcitonin gene-related peptide was also found within terminal buttons of OMES fibers making synapse with OHCs [12,13].

Until now, clarifying that the majority of these neurotransmitters coexist within the OLES was very important [12]. The coexistence of all these neurochemical substances clearly indicates that they probably have some kind of cooperative neurophysiological role during the auditory coding process or the protection of afferent nerve fibers (or both). Therefore, the OLES system clearly constitutes a highly selective filter that modulates the afferent fibers in a manner suitable for each distinct situation.

SYMPATHETIC INNERVATION OF THE AUDITORY RECEPTOR

Cochlear sympathetic innervation mainly originates at the superior cervical ganglion [1,3] or at the stellate ganglion [1,41] and ends by forming a perivascular and spiral lamina network. Cochlear sympathetic innervation mainly contains norepinephrine [32,33,39,42].

Serotonergic Fibers Innervating the Auditory Receptor

The presence of serotonin (5-HT) within the mammalian cochlea was identified in homogenates using high-performance liquid chromatography coupled to electrochemical detection biochemical techniques [43], even though some indirect evidence strongly suggested its presence within the inner ear [44–46]. The 5-HT-containing fibers projecting on the cochlea have been described as a very scarce nerve bundle (which fact could explain why they were never previously found) mainly located at the middle coil. These 5-HT fibers radially traverse the spiral lamina up to the inner spiral bundle under the IHCs. At this region, the 5-HT fibers make contact with IHCs and probably with type I afferent nerve fibers [47]. Because these 5-HT varicose fibers exhibited a highly particular distribution crossing Corti's tunnel and reaching the OHCs [47], the 5-HT fibers are the sole entity that makes contact with both IHCs and OHCs and with type I afferent nerve fibers [47]. At the apical coil, the aforementioned GABA nerve fibers (which were never found to be in contact with IHCs) also traverse Corti's tunnel to reach the OHCs, but GABA fibers radially cross the tunnel, contrary to 5-HT fibers, which follow a spiral pathway.

Brainstem Nuclei Involved in the Serotonergic Innervation of the Auditory Receptor

The origin of 5-HT fibers projecting onto the cochlea has been found at the brainstem. Our findings clearly indicated the presence of 5-HT neuronal bodies at a periolivary region, on the dorsal part of the superior olivary complex, in particular on the superior olive (Figs. 2, 3A, B). At this region, we have found, in consecutive sections, 5-HT-positive neurons (see Fig. 3A–C) and fluorescent neurotraced neurons (see Fig. 3D). The neurons that exhibited a fluorescent fast blue reaction clearly matched with the 5-HT-containing neurons, and both exhibited a similar big multipolar shape. These 5-HT multipolar neurons showed three or four thick principal dendrites that proceeded regularly from round somata in the dorsal region (see Fig. 3). Most of the dendrites were oriented in the lateral and ventral directions, and some of these could be addressed toward the LSO and MSO, but we never observed a direct contact between these dendrites and the LSO and MSO subnuclei.

These neurons have been previously observed; in fact, Warr et al. [48] have shown that the superior olivary complex is surrounded by loosely arranged periolivary neurons that project to the cochlea. Some of these heterogeneous groups of cells were identified as "shell cells" [48,49]. The shell cells project into the rat cochlea, forming the long projection exclusively under IHCs [48,49]. In contrast, Gil-Loyzaga et al. [47,50] showed that inside the cat cochlea, some of these 5-HT fibers, which also innervated the IHCs, used a long

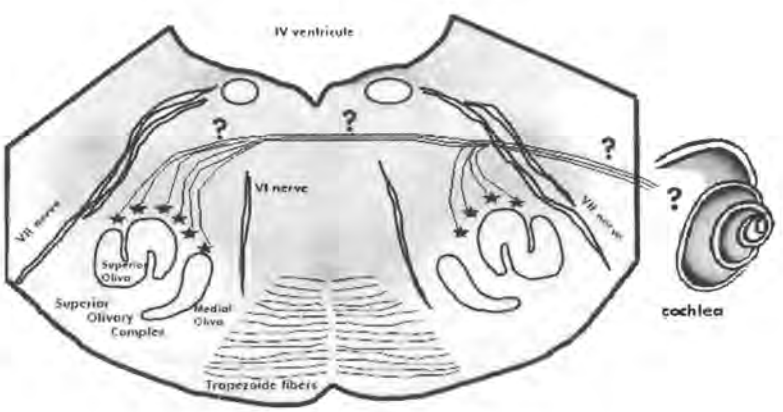

Figure 2. Distribution of serotonergic neurons found bilaterally on the superior olivary complex. Fibers originating from ipsilateral and contralateral neurons reach each cochlea; however, the trajectory that they use (indicated with a question mark) has not been well defined.

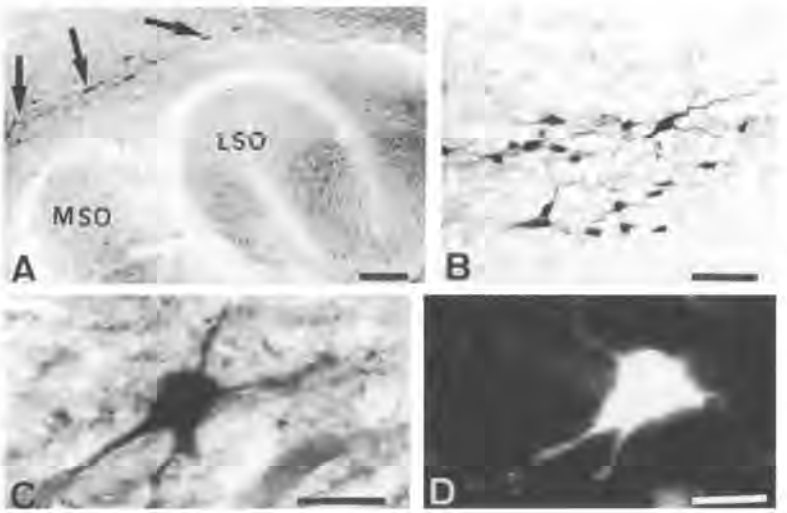

Figure 3. Photomicrographs show serotonergic (5-HT) neurons recognized by immunocytochemistry (A–C) and fluorescent neurons of the corresponding areas labeled by fast-blue (FB) retrograde neurotracer (D). Set of 5-HT neurons located (A) dorsally to the superior olivary complex (SOC; arrows) and (B) rostrally to the SOC. (C) A multipolar neuron of the set dorsally located to SOC. (D) A kind of neuron similar to that shown in part C after retrograde FB neurotracing from the cochlea. (*LSO* = lateral superior olivary subnucleus; *MSO* = medial superior olivary subnucleus.) Scale bars: A, 100 μm; B, 50 μm; C and D, 20 μm.

pathway crossing Corti's tunnel and reaching the OHC area further on. A similar pathway also appeared in a previous schematic published by Warr [2]. However, in that study, these sporadic branch fibers were reported as a part of the olivocochlear lateral efferent system. Probably at the peripheral receptor, the 5-HT fibers are very thin and rare, as was previously reported [47]. Only a highly specific immunochemical detection technique for a 5-HT neurotransmitter could identify such a particular fiber distribution.

At the brainstem, we identified abundant 5-HT varicose fibers into the LSO subnucleus, a result consistent with previous findings [51–53]. The 5-HT varicosities in the LSO could make synaptic contacts with other auditory and nonauditory nuclei [51,52]. In particular, the raphe nuclei may control the level of activity of the cochlear nuclei [52,54,55]. Also, a subpopulation of neurons located within the dorsal raphe nucleus (which probably also contains 5-HT) were neurotraced from the cochlea with cholera toxin-B injected into the inner ear [55].

ROLE OF SEROTONIN IN AUDITORY FUNCTION

Serotonin is a widely distributed neurotransmitter, in particular within the brainstem, considered a major neuromodulator for the mammalian sensory system [56]. The 5-HT neurons have been identified in most mammalian species, including humans, and have been involved in modulation or inhibition of peripheral and central nervous system neurons [55,57–59].

5-HT and its metabolite, 5-hydroxyindole-3-acetic acid, were identified and quantified within the rat cochlea by high-performance liquid chromatography coupled to electrochemical detection [43,50]. Seventy-six percent of the 5-HT cochlear concentration belongs to the blood, and the remaining 24% was found within the cochlear tissue [43]. Some differences between 5-HT concentration in pigmented and albino rat cochleas could indicate the presence of 5-HT in cochlear melanocytes, without excluding interspecies differences [50].

The 5-HT neurons are thought to be involved in many general physiological functions (e.g., sleep, memory, pain, locomotion) [58] but also in auditory regulation [54,55]. Serotonin could be involved in the regulation of sound transduction at the auditory receptor [43]. In fact, 5-HT was considered a modulatory substance of the compound action potential of the auditory nerve [44]. However, the real function of 5-HT within the auditory receptor requires further investigation.

5-HT efferent cochlear innervation could play a particular functional role unlike that of other cochlear efferent neurotransmitters. In particular, the total 5-HT cochlear concentration did not change after acoustic stimulation [43]. However, the blockade of 5-HT transporters by 6-nitroquipazine within the cochlea has demonstrated that this is a functional and active neurotransmitter involved in cochlear physiology [60].

Other 5-HT brainstem neurons projecting onto sensory systems have been involved in such specific roles as alertness, attention, and the like [61]. In addition, a disrupted or modified 5-HT function leads to a loss of auditory filtering and the lack of habituation implicated in tinnitus [62]. Therefore, one could suggest that the 5-HT fibers projecting onto the cochlea from the periolivary neurons might be involved also in alertness, attention, control of sleep and wakefulness cycles, and state of urgency [55,63] in the auditory receptor, contributing to its preparation before or during the transduction process.

The major mammalian auditory brainstem nuclei, inferior colliculus, superior olivary complex, and cochlear

nuclei are also innervated by 5-HT fibers [51–53]. This innervation could be involved in the modulation of auditory functions, in particular in filtering of the auditory message [51–54,63–65]. However, no information is thus far available about the role of 5-HT projecting fibers onto the cochlea [43,47,60]. The fact that 5-HT innervation projects onto active sensory cells and, probably, onto afferent nerve fibers could involve these fibers in the entire regulatory function of the peripheral auditory system. Recently, brainstem serotonergic fibers were found projecting onto ascending and descending auditory pathways [56], which could have functional influence on the entire control of audition similar to that exercised by 5-HT fibers projecting on the cochlea. Alterations of both serotonergic systems coming from brainstem nuclei could be involved in dysregulatory alterations of the auditory process, as in tinnitus. However, future research could be addressed to identify the functional role of these 5-HT fibers in auditory processing, and to clarify the relationship between the superior olivary complex and other non-auditory formations (i.e., raphe nuclei or reticular formation), as regards their involvement in pathological processes.

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