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Transtympanic Pilocarpine in Tinnitus

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Abstract: In 48 patients who had neurosensory hypoacusia and whose main complaint was tinnitus, a 1% pilocarpine solution or a 2% carbachol Isopto solution was placed in the tympanic cavity by means of a No. 26 pencil-tipped lumbar puncture needle through the front quadrant of the eardrum. Patients were chosen without regard for age, gender, or topographical damage of the acoustic pathway. Evaluation of the drug's effect was performed audiometrically by masking with the minimum intensity of the pure sound or narrow band that most closely resembled the patients' own noises. The results of this medical therapy were positive and ranged from complete annulment to attenuation of the tinnitus, which was confirmed by audiometric masking 30 minutes after the intratympanic injection. These positive results reached 50% and would have been higher if the several cases submitted by accident insurance companies and cases of presbyacusia were discarded. The unsatisfactory element of the study was the short-term effect of the therapy, which usually lasted no more than 12–72 hours. Tinnitus reappeared in all patients at its original intensity. The best results involved the use of carbachol as compared with pilocarpine. The decision to replace pilocarpine with carbachol was based on the idea that the inhibitory cholinergic efferent pathways are damaged before the afferent pathways. The use of pilocarpine depends on efficient cholinergic functioning, as its activity is as an indirect agonist (i.e., to annul the cholinesterase enzyme).

Keywords: carbachol collyrium; cholinergic efferents; cholinesterase enzyme; pilocarpine collyrium; transtympanic puncture

In general terms, the theory that nerve efferents extend from the central nervous system toward the aural periphery and control mainly inhibitory function is being accepted widely. This control principally leads to the inner and outer ciliated cells of the Corti organ, the nervous cochlear dendrites, and the muscles of the middle ear, a fact that has been demonstrated indirectly by means of histochemical dyeing of the acetylcholinesterase enzyme, which manifests itself in stimulating the nerve branches of the olivocochlear efferent fasciculus (Fig. 1) [1]. Thus, we would have central controls of the inner and middle ear and a third control, from the sympathetic system, in the vascular bed of both the middle and inner ear. This sympathetic neurotransmitter is discussed later. The efferent olivocochlear pathway, together with its neurotransmitter, acetylbetamethyl choline, which operates on the nicotinic receptors of the outer ciliated cells [2], may be blocked by strychnine and bicuculine [3].

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Our clinical priority is to relieve patients of the symptom of tinnitus, which, in some cases, is insufferable and has even led to suicide. Of a total of 300 patients in our practice who were suffering neurosensory hypoacusia due to various causes, 50% of the patients' primary complaints were of tinnitus, not hypoacusia.

We proceed on the basis of three known viewpoints: (1) that it is possible pharmacologically to influence the function of the inner ear through to the round window (anesthetics, ototoxic agents, etc.) [4]; (2) that tinnitus is an abnormal sign of the function of any organ of the acoustic pathway; and (3) that an efferent control pathway with inhibitory qualities is active with cholinergic neurotransmitters on nicotinic receptors, with which control of tinnitus might be possible. We know that physiologically normal efferent pathways have no control over tinnitus; instead, they have a more complex function, including selecting, filtering, and reinforcing certain frequencies, as opposed to other frequencies, so as to understand the acoustic world better [5].

Our study was undertaken to emphasize the cholinergic inhibitory action of the efferent pathway, the neural somatic seat of which is found in the nuclei of the

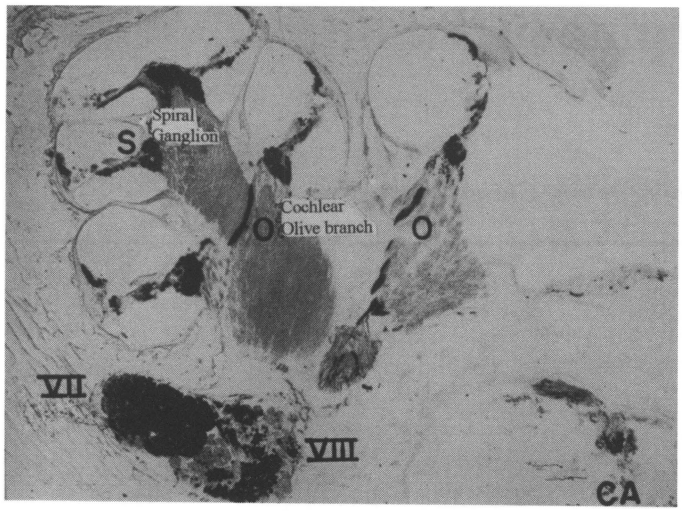

Figure 1. Histochemical dyeing reveals acetylcholinesterase enzyme activity in stimulating the nerve branches of the olivocochlear efferent fasciculus. (Reprinted from K. Balogh, Y. Nomura, A technique for the demonstration of acetylcholinesterase activity in the inner ear after decalcification with EDTA. *J Histochem Cytochem* 12:931, 1964.)

higher oliva of the brainstem [6]. We began by placing in the round window a known drug that annuls the action of cholinesterase, which simultaneously destroys acetylcholine while reinforcing the action of this acetylcholine on the Corti organ. The drug we used was simple pilocarpine collyrium, which is used widely by ophthalmologists; later, this was replaced with carbachol collyrium, following the ophthalmologists' criterion to reinforce directly the acetylcholine that does not necessarily annul the already diminished enzyme cholinesterase.

MATERIALS AND METHODS

Under local topical tympanic anesthesia with Bonain liquor, approximately 0.60 ml of 1% pilocarpine collyrium was injected through the tympanic membrane in its front quadrant with a pencil-tipped No. 26 lumbar puncture needle and a tuberculin syringe. At a higher concentration of the drug, the patients complain of pain. During the last operations, as the patients felt well, anesthesia was unnecessary, as puncture of the case mucosa is more annoying than painful.

Patients lie supine with the head slightly turned toward the side opposite the ear that is being treated. Among all operated patients, change in the inhibitory effects of the pathway reached a mean of 43 dB. Patients were not subclassified according to the probable point of origin of tinnitus along the acoustic pathway, gender, age, or other parameters.

To ensure the true effect of the medication through the round window, all patients were asked to match their tinnitus with a pure tone or narrow-band mask; they were not asked to describe the sound of their tinnitus. This practice served to measure tinnitus intensity. Moreover, 5 dB could be added to the audiometric sound over the intensity of tinnitus that the patients indicated. In this way, we attempted to ensure that patients would not hear their own sound, and we could not project with certainty the minimum intensity necessary to annul the tinnitus. After half an hour, patients were subjected to another audiometry reading, and the minimum sound intensity necessary to annul the tinnitus was measured again, without regard for patients' reports that they heard their tinnitus with a lower intensity. As the frequency of the original tinnitus already had been logged, a reading of the true effect of the drug on tinnitus could be ensured.

RESULTS

The 46 patients with tinnitus who were selected for the experiment (Table 1) were informed about its purpose and about the risks involved, according to the specifications of the ethical rules of the Medical College of Chile. Patients agreed to the operative procedure. Discrimination of the pathological processes was restricted to neurosensory hypoacusia. Some of the patients complained of tinnitus after encephalocranial trauma (head injury), were affiliated with accident insurance companies, and expected compensation; these patients agreed to participate in the hope of confirming their case. Of these, only one obtained beneficial results.

In all patients with a clear pathology of labyrinthine hydrops, symptoms were alleviated either temporarily or permanently. However, the most surprising occurrence was a case of an old lesion incurred by head injury and atrophy of both temporal lobes, in which tinnitus disappeared for 12 hours. In most patients, the tinnitus did not disappear completely; rather, it decreased in intensity.

Table 1. Transtympanic Pilocarpine Effect in Tinnitus

Patient No.	Name	Age (yr)	Diagnosis	Pretherapy Tinnitus Level (dB)	Posttherapy Tinnitus Level (dB)	
					Immediate	Day 2
1	AAJ	45	Head injury		40	Annulled
2	PPJ	60	Hypertensive encephalopathy	65	55	65
3	MAR	50	Head injury	80	80	80
4	ZHM	35	SHL	50	20	15
5	ZCA	28	Paraplegia	30	30	30
6	VSJ	45	Chronic OM	90	20	20
7	VAV	55	Lacunar infarction	60	40	40
8	RAJ	60	Acoustic trauma	55	55	55
9	RSJ	53	SHL	90	95	60
10	OOR	40	Head injury, ins	55	55	55
11	MFJ	52	Head injury, ins	65	65	65
12	MAL	49	Head injury, ins	70	70	70
13	CRJ	47	Head injury, ins	45	45	45
14	MBH	60	Chronic arterial hypertension	60	Annulled	Annulled
15	FMC	41	Acoustic trauma	35	15	15
16	CCM	68	DM	40	40	40
17	CSC	50	Acoustic trauma and head injury	75	75	75
18	ACM	38	Acoustic trauma by explosives	30	Annulled	Annulled
19	SML	55	Acoustic trauma	75	Annulled	Annulled
20	SAS	57	DM and streptococcal infection	65	65	65
21	RME	58	Acoustic trauma and high lipidemia	80	80	80
22	POH	57	Acoustic trauma	70	40	40
23	PRC	52	Chronic OM	110	90	90
24	FRO	67	High lipidemia	75	30	30
25	DML	53	Chronic OM	70	70	70
26	CMR	36	Ménière's disease	50	Annulled	Annulled
27	CCG	72	Presbyacusia	55	50	50
28	VLR	65	Acoustic trauma	75	75	75
29	VVD	48	Acoustic trauma	60	25	25
30	VSC	56	Acoustic trauma and chronic OM	45	Annulled	Annulled
31	SUA	25	SHL	55	55	55
32	SCE	74	TMJ syndrome	45	Annulled	Annulled
33	SVV	39	Acoustic trauma	65	30	30
34	RVJ	30	Chronic OM	65 Carbachol collyrium	40	40
35	JAR	82	Chronic OM and presbyacusia	90	40	60
36	BJV	55	SHL	65	Annulled	Annulled
37	SBA	43	Ménière's disease	45	65	Annulled
38	VAV	55	Uricemic gout	60	50	50
39	KRA	76	Ménière's disease	65	65	Annulled
40	HSH	56	Hypertensive encephalopathy	100	100	65
41	NMA	56	Uricemic gout	65	65	65
42	AOV	41	Acoustic trauma	85	75	70
43	MLL	36	Ménière's disease	65	70	70
44	CJM	65	Presbyacusia, BPPN	50	Annulled	Annulled
45	RTM	76	Cervical arthrosis	65	35	65
46	PHA	67	Chronic OM	80	Annulled	Annulled

BPPN = benign paroxysmal positional nystagmus; DM = diabetes mellitus; ins = insurance (i.e., patient referred by insurance company); OM = otitis media; SHL = sudden hearing loss; TMJ = temporomandibular joint.

In general, a mean of 60-dB-intensity tinnitus diminished to 40 dB after the operation. From the patients' perspective, this is important, as a decrease of 20 dB at very strong intensities is significant. The duration of the effect of pilocarpine ranged from 12 to 72 hours.

A grommet with a hole was placed in the eardrum of one patient, at her request, as she could not return for another dosing because she lived far from the city; the hole permitted her to drip into the ear a solution of pilocarpine collyrium every 3 days for several months.

The patients showed gyrator vertigo with both drugs used. The nystagmus observed was toward the contralateral ear and lasted from 15 to 20 minutes.

DISCUSSION

Several basic points were considered in our proposal of a direct pharmacological treatment in the inner ear. First were the numerous bibliographical citations by authors who have been studying the inhibitory effect of efferent pathways, the main chemical basis of which is the acetylcholine found along the entire efferent acoustic inhibitory pathway from the front lobule to lower centers [7]. Second was knowledge of the physiological mechanism that refers to sonority of the stimulus toward higher auditory centers in experiments that show this discriminating function of the olivocochlear efferent neurons to improve from a silent environment to a noisy one [8]. According to some studies, afferents play a physiological role in improving sound discrimination but do not annul a noisy "artifice," such as tinnitus [8]. Our experiments take advantage of this inhibitory mechanism, even though it would not be possible to annul tinnitus completely. Finally, available data on the influence of ototoxic drugs, anesthetics, hypertonic solutions, vasodilators, corticoids, and other drugs on the cochlear function, through the round window, suggested the choice of pilocarpine in a collyrium solution because it is accessible, low-cost, and stable, and has a known effect of annulment of the cholinesterase enzyme.

During these experiments, the absence of patients younger than 18 years was noted. In fact, the number of patients increased in proportion to increasing age. The activity of acetylcholine would be expected to be declining in persons as they age, but acetylcholinesterase would disappear first, as the need for inhibitory effects would be less as hearing is impaired.

Pilocarpine was later replaced with carbachol collyrium, a synthetic acetylcholine, to support the inhibitory effect of acetylcholine directly rather than to annul the destructive enzyme, as very little of the enzyme would remain to be inhibited. According to our results, carbachol is more effective then pilocarpine.

A question remains: Though positive results were achieved, what is the purpose of a palliative and intervening treatment such as transtympanic pilocarpine, even if it is innocuous, if its effect is bound to last only 24–72 hours?

Our pharmacological investigation demonstrates a different but clear example of an effective agent, centered around acetylcholine, in the treatment of tinnitus. Other research that we have conducted has revealed that indirect agonist acetylcholine drugs, such as tacrine, do not diminish tinnitus in the few patients on whom we have used them.

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