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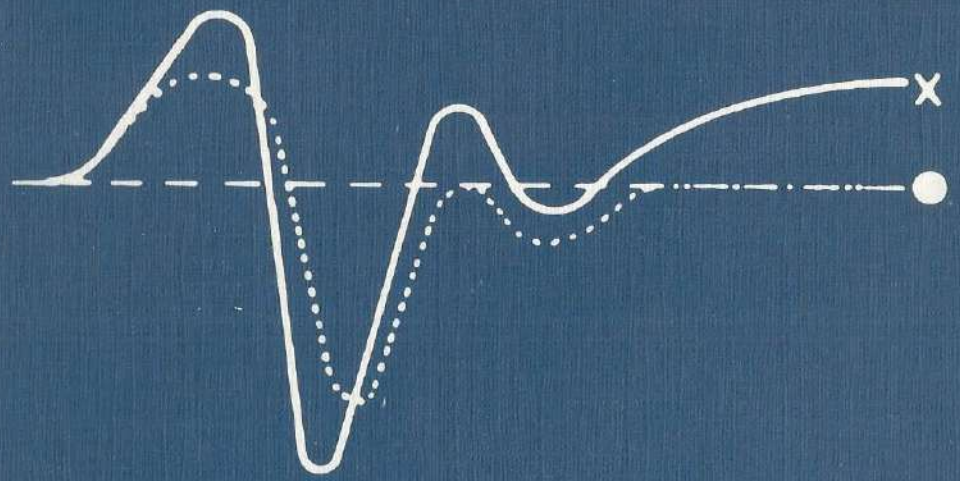
BEREND EBO GLAZENBURG



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Het in dit proefschrift beschreven onderzoek werd verricht in de afdeling Keel-, Neus- en Oorheelkunde van het Universitair Medisch Centrum te Leiden.
Het manuscript werd getypt door Mej. M.C. Kanbier en Mej. E.A.M. Stuurman. De figuren werden getekend door de Heer J.J. Magdelijns en de Heer J. van Leeuwen van de audiovisuele dienst van het Universitair Medisch Centrum te Leiden en de Heer J. Tinkelenberg van de afdeling Anatomie der Rijksuniversiteit Leiden. De electronische apparatuur werd in eigen werkplaats vervaardigd en beheerd door de Heer A. van Wijngaarden. De electroden werden geprepareerd door de Heer R. Kamerling. De proefdierenafdeling werd beheerd door de Heer J.C.N. van de Ploeg en de Heer G. Kok.

Aan mijn ouders

I Acoustic neurinomas

1.1 Introduction

The diagnosis of a tumor in the brain occasionally presents a problem. The diagnosistic problem may become complex when the space occupying process is located in a so-called silent area of the brain. Regions with poor diagnostic symptoms are the frontal lobe and the cerebellopontine angle. *The aim of this study is to make a contribution to the diagnostic tools, which are available to the otoneurologist in his search for cerebellopontine angle processes and especially for acoustic neurinomas.*
In man, acoustic neurinoma accounts for about one half of the space occupying lesions in the cerebellopontine angle. Of all intracranial tumors approximately 8% originate from the eighth nerve (Gussen, 1975). The remaining pathology of space occupying processes in the cerebellopontine angle is formed by tumor metastasis of for example mamma-carcinoma (Niedermowe, 1953), carcinoma of the prostate (Novotny, 1918), bronchus carcinoma (Goldschmidt, 1959), thyroïd tumor (Carco and Motto, 1958) and kidney carcinoma (Oppikofer, 1931).
Primary space occupying lesions in this area might be due to meningiomas (Merrit, 1959), primary cholesteatoma (Hitselberger and House, 1971), arachnoid cysts (Evans, Courville, 1932), vascular aneurysm and gliomas (Davey, 1932) and neurinomas of the fifth and seventh nerve (Kemp, 1964).
The acoustic neurinomas have been exhaustively studied, clinically, anatomically, histologically and surgically. In a historical review about the diagnosis and treatment of acoustic neurinoma Glasscock (1968) states that the first postmortem description of an acoustic neurinoma has been given by Sandifort of Leiden, Holland in 1777. Important contributions to the study of these tumors were made by Verocay (1908), Henschen (1915), Cushing (1917), Dandy (1925), Pool and Pava (1957), House (1964) and Nager (1969).

1.2 Origin of the tumor

Acoustic neurinomas are benign encapsulated tumors, that arise as a result of neoplastic proliferation of Schwann's sheath cells of the eighth cranial nerve. There are two schools of thought about the cell of origin of these tumors, namely the Schwann cell and the perineural cell (Cravioto, 1969). The differentiation between these cells is made on basis of their location along the eighth nerve. (Harkin and Reed, 1969). Both cells have a common origin from the acoustical-facial ganglion (Henschen, 1916). A direct anatomical contact between spiral ganglion cells and Schwann's cells has been demonstrated in the adult cat (Adams and Daigneault, 1972).

The most frequent site of origin of the acoustic neurinoma is the vestibular division of the eighth nerve in the region of Scarpa's ganglion (De Moura, 1967). This origin is supposed to be explained by the excess of sheath cells in the vestibular nerve as compared to the cochlear nerve (Skinner, 1929). The most vulnerable area of developmental autonomic growth is considered to be the zone of transition from central myelin to peripheral myelin (Gussen, 1975).
This area is located within the internal meatus near Scarpa's ganglion. Because of the site and the originating cell structure the description as vestibular schwannoma or vestibular neurilemona have been suggested (Nager, 1969, Schuknecht, 1974). However, various sites of origin and location have been described, ranging from the middle ear (Storrs, 1974) up to the cochlea (Karlan, 1972) and labyrinth (Wanamaker, 1975, Jorgensen, 1962). Bilateral occurrence is rare, up,to 2-4% of all acoustic neurinoma cases (Schötzle and Haubrick, 1975). Bilateral acoustic neurinomas are mostly found in systemic disease as von Recklinghausen disease, central nervous dysplasia and Turner-Gardner-Syndrom (Hitselberger and House, 1968, Linthicum, 1972, Gardner and Frazier, 1930).

1.3 Macroscopic and Microscopic Appearance

Acoustic neurinomas are encapsulated tumors, that grow by direct volume expansion, compressing and distorting the surrounding structures.
The capsule is formed by compressed perineural tissue. The growth rate is supposed to be very slow, but no exact data are available.
On macroscopic inspection the external surface of the tumor is firm and irregular, sometimes thin walled cysts are present. Histological examination of an acoustic neurinoma shows a quite characteristic pattern. As it takes its origin from supporting cell structures the tumor contains no nerve fibers.
The tumor is characterized as a so called Antoni type A (Antoni, 1920) if it contains densely arranged slender elongated cells with some chromatin in their nuclei surrounded by hyalin fibers. Typical palisading of nuclei is sometimes found, in which they lie parallel, side by side, separated by hyalin fibers. These characteristic zones in the tumor are known as Verocay bodies.
Antoni type B is characterized by abundant intracellular material, which stains poorly. In contrast to type A, here the cells have distinct cytoplasmic outlines.

1.4 Clinical signs and symptoms

From the vast extent of data published about acoustic neurinomas it seems impossible to correlate size and location with the clinical symptoms. This might be partially explained by the fact that in many clinical studies no exact information is given about the precise location of the tumor. Also the extension and size of the tumor often makes an exact description impossible. Otherwise small and medium sized tumors rarely present the typical clinical picture and large tumors may even fail to produce all the anticipated findings (Sheehy, 1968). Another problem in correlating tumor size and location with clinical symptoms, is that several completely asymptomatic acoustic neurinomas located within the internal auditory canal have been

described (Scott, 1938, Hardy et al., 1936). In routine histopathological temporal bone studies an incidence as high as 0.9% of asymptomatic acoustic neuroma was found (Leonard et al., 1970, Schuknecht, 1974).
When the tumor is located in the internal meatus, a so called lateral acoustic neurinoma (Graf, 1952, 1955), compression of the eighth nerve may occur with widening of the internal meatus. Widening of the internal meatus is due to bone demineralisation caused by direct tumor compression and ischemia. It is a frequent observation in intracanalicular tumors (over 90%), and probably not found in relatively vast growing tumors and those neurinomas that originate outside the internal auditory meatus (Sterkers, 1975).
Compression of the eighth nerve and the arterial blood supply to the cochlea causes degenerative changes within the membranous labyrinth, which may result in atrophy of the stria vascularis and loss of hair cells (De Moura, 1967). The observed changes within the cochlea and labyrinth may help to understand the clinical signs and symptoms. Early symptoms of a tumor confined to the internal auditory meatus include tinnitus, unilateral hearing loss, and dizziness.

The most consistent early symptoms are slight high frequency unilateral hearing loss and tinnitus. True vertigo is uncommon, in about 80% of the patients complaining of dizziness it appears in a form of unsteadiness with walking (Pulec et al., 1964, Hitselberger and House, 1971).
However so many disorders may present with hearing loss, tinnitus and dizziness, that the differential diagnosis can be very difficult.
The late manifestations of an acoustic neurinoma develop with extension from a laterally situated tumor out of the internal meatus (8 mm), followed by pressure-effects of the surrounding structures, for example the fifth and seventh cranial nerve.
Although compression of the facial nerve may occur at an early stage, functional impairment as facial motor weakness always is a late symptom. The sensorial fibers have a smaller diameter and are therefore less resistant towards stretch and compression by the expanding process (Sterkers, 1975).
Total deafness with intact cochlear nerve can be caused when the arterial blood supply is compressed by the tumor. Through the close relation between the tumor process and the middle cereballar artery, there is always the risk of disruption the arterial blood flow to the cochlea during surgical removal of the tumor.
Arterial compression by the tumor process may also lead to ischaemic infarction in the oblongate medulla and pons. Finally with further progress of the expanding tumor process the IVth ventricle may be compressed, causing obstruction of cerebrospinal fluid circulation, in a so called obstruction hydrocephalus. The increased intracranial pressure will damage the brain, and blurred vision may occur as a symptom of optic nerve degeneration (Merrit, 1959).

The diagnostic screening tests in any patient suspected of a possible cerebellopontine angle tumor are shown in table I.

Table I

Neuro-otological history	Tinnitus, hearing loss, vertigo, headache, vomiting, cerebellar symptoms, dysarthria, seizures.
Neuro-otological examination	V, VII, IX, X cranial nerve. Increased C.S.F. proteïn.
Auditory screening	Unilateral high frequency hearing loss. Poor speech discrimination. Békésy type III, IV. Abnormal tone decay, Stapediusreflex, abnormal reflex decay. Brainstem responses: delay in I-V latency Electrocochleography: broad AP-waveforms
Electronystagmography with Caloric Testing	hyporeactive labyrinth. Central lesions.
Radiographic examination	Stenvers, Steenhuis projection: widening of the internal acoustical canal. Posterior fossa Cisternography: filling defects. Brainscan: mass in the cerebellopontine angle.

Various specific tests can be helpful in certain cases, like a diagnostic labyrinthotomy in doubtful cases or during operative procedures for Menière disease. Sometimes to rule out an acoustic neurinoma an arteriogram or venogram will be necessary (Kosoy, 1977).
The liability of the various diagnostic screening tests as presented in TABLE I, has been reviewed in the literature.
Generally the routine audiometry shows the classical findings in only about half of the patients with an acoustic neuroma (Johnson, 1966, 1968, 1977, Flower, 1961). With the introduction of the Stapediusreflex- and decay test the results of audiometric screening tests have improved. In general these auditory tests have a greater validity in series with larger, and medium sized tumors as compared to small tumors (Johnson, 1968). This is probably explained by the fact that small tumors as originating from the vestibular nerve, have not yet reached the cochlear branch of the eighth nerve, to produce any audiotory symptoms.

In the recent literature data have been published about the electrical responses as generated by the cochlea, the eighth nerve and the brainstem in retrocochlear pathology. (Aran et al., 1973, Morrison et al., 1976, Odenthal and Eggermont, 1976 a, Portmann, 1973, Selters and Brackmann, 1977). The value of these tests in the diagnosis of retrocochlear lesions will be discussed in Chapter X.
Vestibular function tests are accurate and useful in the diagnosis of acoustic neurinomas (Rademakers, 1973). According to the literature the caloric test is found to be abnormal in about 90% of the patients with acoustic tumors. The small and more laterally situated tumors are more likely to present with hypo- or non reactions in the caloric tests.
Larger and medially situated tumors will show the characteristics of a 'central lesion' in the various tests.
The radiological examinations of the temporal bone include the use of special headsets and projections as the Raw, Chamberlain-Towne and Stenver's view.
A difference of 2 mm in the width of the canals is considered significant and indicates widening by erosion of the internal audiotory canal (Valvassori, 1969).
Others consider 1 mm difference as abnormal (Sheehy, 1968). Cisternography is the most reliable and conclusive test to rule out a process that is either located in the cerebellopontine angle or the internal auditory meatus (Valvassori, 1969).
In experienced hands the positive contrast study of the posterior fossa is a safe technique. In 100 patients, subjected to this method no complications were reported (Scanlan, 1964), and in 827 patients spinal headache and back and legache were reported in less than 5%, while no serious complications did occur (Britton et al., 1968). The clinical experience with computerized tomography in the diagnosis of acoustic neurinomas is limited.
False negative findings are unacceptably high in the presence of small lesions due to the unreliable technique for delineating the size and configuration of the internal auditory canal (Hoffman and Cox, 1977). Like most of the diagnostic screening tests it should be used as a helpful test among other tests (Bergeron et al., 1977, Messina, 1976).

1.5 Treatment of Acoustic Neurinomas

The emphasis of the underlying study is mainly on the diagnostic aspects of acoustic neurinomas, therefore, the surgical treatment of these tumors will be only briefly reviewed here, from a historical point of view.
The first successful removal of an acoustic neurinoma was done in 1894 by Sir Ballance. The post-operative complications consisted 'of fifth and seventh cranial nerve palsy and enucleation of the right eye was inevitable, but, 'the patient was well and alive'.
At the turn of the century the treatment of choice was through a bilateral suboccipital approach with tumor removal by finger dissection (Horseley, 1900, Krause, 1903). The post-operative mortality ranged from 60-85%, because patients were generally operated on at a very late stage, having increased intracranial pressure, which could not be controlled. A technique of suboccipital approach combined with bilateral decompression operation and subtotal tumor removal reduced the operati-

on mortality from 80% to 20% (Cushing, 1917). Around 1930 the diagnostic tests for acoustic had been greatly improved and tumors could be operated on at a much earlier stage. The location of the site of the tumor introduced the unilateral suboccipital approach and operation mortality was further reduced (Dandy, 1935).
Up to 1950 no new contributions to the surgical treatment of posterior fossa tumors were made. A problem in the suboccipital approach for acoustic neurinoma is that the brainstem structures in the posterior fossa don't tolerate much manipulation. Post-operative bleeding and edema are responsible for the high operation mortality by this technique. Another problem posed by this approach is that the internal auditory canal and the facial nerve can only be visualized after substantial tumor removal. Therefore the facial nerve is often injured or destroyed during the operation.
In 1940 the problem of the facial nerve was recognized by Olivecrona who tried and succeeded to save the nerve with removal of the tumor.
In 1949 the close relationship of the middle cerebellar artery to the cerebellopontine angle tumors was recognized, which reduced the life threatening post-operative complication of bleeding in the posterior fossa (Atkinson, 1949).
The modern era of acoustic neurinoma surgery was started in the late 1950's.
For total exposure and grafting of the facial nerve in patients with temporal bone trauma the so called middle fossa approach had been introduced (Clerc, 1954, Guillemin, 1960). It was not until House described his surgical technique and instrumentation for middle cranial fossa surgery in the early 1960's, however, that this technique became generally accepted in surgery for acoustic neurinomas (House, 1961, 1962, 1964). The major advantage of this technique is that direct visualization of the facial nerve is possible and that the serious complication of the suboccipital approach can be avoided.
Now this technique has proven its usefulness in surgery for acoustic neurinoma (House, 1968, Fisch, 1970), vestibular nerve section (Fisch, 1971), facial nerve decompression (Pulec, 1969 a) and surgery for tumor of the Vth and VIIth cranial nerves (Pulec, 1969 b). The limitations of the middle fossa approach for the removal of acoustic tumors, however, soon became apparent. The exposure is inadequate for the removal of larger tumors, that extend into the cerebellopontine angle (House, 1964).
A new approach was developed, which enabled excellent visualization of the anterior and lateral aspect of the tumor and direct exposure of the facial nerve. This can be achieved by the so called translabyrinthine approach (House, 1964).
In 1912, the first succesful transbyrinthal tumor removal was done in the Netherlands by Quix, 135 years after the first description of this tumor by his countryman Sandifort (Shambaugh, 1970).
By this technique there are practically no limitations to the size of the tumor and extension behind the sigmoid sinus is possible. The translabyrinthine approach is the treatment of choice for those tumors that extent medial to the internal auditory meatus into the cerebellopontine angle. For small tumors, that extend just out of the internal audiotory meatus the middle fossa approach can be used.
In case of larger tumors with increased intracranial pressure a combined technique can be used, with translabyrinthine and suboccipital approach, since then a suboccipital decompression can be a lifesaving procedure.

The serious complications of surgical removal of these large tumors clearly demonstrate the great desirability of early diagnosis of acoustic neurinomas, since the new surgical techniques show fewer complication and offer the possibility to save facial nerve function.
In these days surgery for acoustic neurinoma has advanced from a life saving procedure to prevent death from increased intracranial pressure to a delicate problem of total tumor removal, which aims to restore eighth nerve function (Innitzer, 1976 a, Glasscock, 1978). To achieve this, early diagnosis of acoustic neurinomas at the time they are still confined to the internal auditory canal is necessary; to quote the pioneer of modern acoustic neurinoma surgery: 'our diagnostic methods must be greatly improved, and this is one of our most important tasks for the future' (House, 1964).
This statement is well illustrated (House, 1968) by the fatalities in acoustic neurinoma surgery. In a total series of 200 cases the fatality was 14, or 7% (House, 1964). Of these tumors 64 were classified as large tumors with a fatality rate of 17%, which had to be approached by the combined suboccipital-translabyrinthine approach. Of this series 5 tumors were classified as small acoustic neurinomas and could be removed by middle fossa approach. No fatalities were seen in this serie.
In a serie of 36 patients operated by the translabyrinthine technique no fatalities occurred, and, facial nerve function was preserved in 22 patients (61%). (Glasscock, 1973). In a series of 75 patients using the translabyrinthine approach for small tumors (< 2.5 cm), and a combined translabyrinthine suboccipital staged operation, for large tumors (> 2.5 cm), there was an incidicence of 18% permanent facial paralysis (Montgomery, 1973). In a series of 16 patients operated on the suboccipital technique one death was reported (Smith, 1973).
Both techniques have their supporters nowadays and from the recent literature it is difficult to say which should be preferable. Besides operation mortality, facial nerve function and preservation of hearing should be considered, and, from the recent literature it is difficult to tell which technique should be preferred.
Advocates of both surgical techniques agree, however, on the importance of early diagnosis at the time of removal and the use of an operation microscope.

II Animal model for acoustic neurinoma

The subject of this study is the evaluation of electrocochlear responses in retrocochlear lesions, with special interest in acoustic neurinomas. A technique will be described to mimic the effects produced by a retrocochlear process in the guinea pig. The experimental model for an acoustic neurinoma could be the application of localized pressure on the eighth nerve, for example in the internal meatus. Local pressure on a peripheral nerve can produce a block of the nerve fiber impulse. The failure to conduct an impulse during local pressure is believed to be due to local anoxia.
To study instant effects of localized pressure on the eighth nerve as an experimental model for acoustic neurinoma, a silicone balloon, used as a volume expander in the internal meatus, was used in cats (Chinn and Miller, 1975). Reversible experiments were carried out by in- and deflating air into the balloon. In recording evoked potentials from the contralateral primary auditory cortex after homolateral pure tone and click stimulation of the cochlea, a marked amplitude reduction was found with balloon placement ('contact phenomena'). The average reduction in the evoked potential due to placement of the silicone balloon was 29%. The authors state that this reduction was not strictly due to pressure effects, since 'very gently placementof pieces of silicone sheeting alone resulted in a substantial reduction' (40%). No further explanation about the contact phenomena is given. During inflation of the balloon a further reduction of the evoked potential was found.
This observation might be explained on the basis of temporary ischaemia. During balloon inflation also a latency increase was found. No latency increase was demonstrated with amplitude reduction due to the contact phenomena.
The effects on latency and amplitude during balloon inflation were found to be reversible.
To explore an experimental model for acoustic neurinoma some pilot studies were done in guinea pig. The separate course of the cochlear and vestibular nerve enables selective experiments on either nerve. Because in man an acoustic neurinoma mostly originates from the vestibular nerve it is of importance to study the effects of selective experiments on the vestibular nerve. In these pilot studies it was found that minimal manipulation ('contact phenomena') of the vestibular nerve resulted in a marked change in the recorded response. The placement of a silicone balloon in the cerebellopontine angle, would exert pressure effects on both the vestibular and cochlear nerve, and the study of the separate effects on either nerve would be impossible. The pilot studies have shown a dramatic effect on the vestibular nerve itself, therefore the use of a balloon was disregarded in studying the electro-cochlear effects of experimental acoustic neurinomas in guinea pigs.
Then a technique was designed to mimic the effects of acoustic neurinomas by applying local stretch on either the vestibular or cochlear nerve selectively.
The pressure effects of an acoustic neurinoma, which optionally may cause a complete loss of nerve conduction were analyzed by selective nerve transection and by KCl block.
In reviewing the results of the first experiments on eighth nerve section a possible role is suggested for the efferent innervation (Fisch and Ruben, 1962). In order to interpret these results the recent knowledge about the anatomy and physiology of the efferent innervation will be briefly reviewed.

III The anatomy of the efferent innervation in guinea pigs

In 1942 Rasmussen described centripetal fibers to the cochlea in cats and recognized their nature as efferent nerve fibers. The efferent nerve fibers have their origin medial to the accessory olive and proceed to the contralateral cochlea. In cat these nerve fibers are about 500 in number and will be referred to as the Crossed Olivo Cochlear Bundle (COCB) (Gacek and Rasmussen, 1961). The COCB is part of the descending acoustic pathway which projects from the auditory cortex to the medial geniculate body and the inferior colliculus. From the inferior colliculus fibers project to various nuclei around the accessory olive complex.
The level of decussation of the COCB is at the floor of the IVth ventricle at the rostral border of the facial genu. In 1960 Rasmussen described a second group of efferent nerve fibers, that are supposed to originate in the S-segment of the olive and proceed to the ipsilateral cochlea. This group of nerve fibers will be referred to as the Uncrossed Olivo-Cochlear Bundle (UOCB). The homolateral fibers, about 125 in number in cat (Gacek and Rasmussen, 1961) join the crossed bundle lateral to the outgoing facial root (Rasmussen, 1958). The origin of the UOCB is not definitely settled. According to Rossi and Cortensina (1963) the UOCB would take its origin between the medial and lateral preolivary nucleï.
These investigators also describe a reticulo-cochlear efferent bundle as part of the UOCB. A similar observation was made by Warr (1975). Using a method of retrograde transport and measuring the horse radish peroxidase uptake Warr estimated a number of 1700-1800 cochlear efferent neurones. Approximately 60% of these neurones originate from the homolateral side. In his original study Rasmussen (1942) found approximately 400 axons from the contralateral superior olivary complex and about 100 from the homolateral superior olivary complex. These new data show that the efferent innervation is much more abundant than previously thought, especially for those originating on the homolateral side.
The efferent fibers of COCB are easily followed as they pass as a small discrete bundle through the vestibular nerve (Spoendlin, 1969, 1975). The efferent fibers leave the vestibular nerve at its distal extremity at the inferior border of the saccular ganglion (Rasmussen, 1953). They pass into the cochlear nerve at the vestibulocochlear anastomosis also known as Oort's anastomosis (Morisson, 1975, Terrayama et al., 1971). The olivocochlear bundle consists of a mixture of myelinated and unmyelinated nerve fibers. The ratio of the number of myelinated and unmyelinated fibers is approximately 3:2 (Terrayama et al., 1969) which was confirmed by Warr (1975). Unfortunately the exact distribution of unmyelinated and myelinated efferent nerve fibers on the inner and outer hair cells is not known.
The efferent nerve fibers entering the cochlea between the basal and second turn

then proceed as the intraganglionic spiral bundle (I.G.B.). The I.G.B. splits up into the inner spiral bundle (I.S.B.) and spiral tunnel bundle. The I.S.B. proceeds towards the Inner Hair Cells (I.H.C.), while the spiral tunnel bundle passes along one to four pillar cells before crossing the tunnel of Corti as the upper and basal radial tunnel bundle (Wright and Preston, 1973). No synaptic interaction between the spiral tunnel bundle and the afferent neural elements could be demonstrated (Wright and Preston, 1975). The efferent axons in the I.S.B. and the spiral tunnel bundle are small fibers approximately 0.1μ in diameter (Smith, 1968).
Whether there is a direct synaptic contact between the I.H.C.-cells and the efferent nerve endings remains still a matter of discussion, but extensive axodendritic synapses with afferent fibers have been demonstrated (Smith, 1961, Smith and Rasmussen, 1963). The granulated nerve endings at the base of the O.H.C. belong to the efferent nerve endings (Engström, 1958).

In guinea pig 10-15% of the cochlear afferents innervate the outer cells, the remaining 85-90% of afferent fibers innervate the inner hair cells (Morrison et al., 1975). As has been shown by transection studies of the COCB in the floor of the IVth ventricle the outer hair cells are mainly innervated by the crossed efferent fibers (Iurato, 1976, Terrayama, 1971).
In cat it was found, however, that also a number of crossed efferent fibers supply the inner hair cells (Spoendlin, 1969). The efferent innervation is most dense in the basal part of the cochlea and the first row of the outer hair cells has the most extensive efferent innervation (Spoendlin, 1967). Each outer hair cell receives six to eight efferent nerve endings. The efferent ending on the outer hair cells has been studied in great detail (Engström, 1966, Kimura and Wersäll, 1962, Iurato, 1962).
A schematical representation of the efferent nerve innervation of the cochlea is shown in Fig. 54.
A postsynaptic membrane at the base of the outer hair cell is found to be present in the area of the vesiculated efferent nerve endings.
No direct contact between the efferent nerve endings and the inner hair cells has been shown, but it was found that in the region of the inner hair cells the efferent fibers were mainly in contact with other afferent nerve fibers (axodendritic) and only exceptionally with the hair cell itself.
Since in the present thesis an animal model is used to study the electrocochleographic data in man it should be noted that the presence and distribution of efferent innervation in man are similar to the various experimental animals described here (Gacek, 1961).

IV Efferent innervation – experimental data

4.1 Introduction

The first experiments on transection of the eighth nerve (= cochlear + vestibular nerve) without severing the cochlear blood supply and recording the various electrical responses were published by Fisch and Ruben in 1962. Previously it has been demonstrated that disrupting the arterial blood supply to the cochlea or the death of the animal resulted in a rapid disappearance of the recorded response (Derbyshire and Davis, 1935). In the experimental model of an acoustic neurinoma, the results of selective cochlear and vestibular (efferent) nerve section and stretch will be studied. To interpret these results a review will be given about the available experimental data on efferent innervation.

4.2 Transection Experiments

4.2.1 Electrophysiology

To evalute the results of efferent nerve section, the findings after section afferent and efferent nerve fibers will be discussed in this section. In recording from the round window the effects of whole nerve section upon the cochlear microphonics (CM), the amplitude of the action potential (AP) the latency of the first peak of the action potential (N_1), and also the influence on the shape of the recorded action potential was studied (Fisch and Ruben, 1962). After transection of the eighth nerve no change was found in the CM. The amplitude of the N_1 component showed a decrease up to 60-80% of the original value in recording from the round window. The second component in the recorded response, the N_2, was still partially present after eighth nerve section (N_2 reduction 35%-55%). Because disruption of the afferent flow by transection of the nerve, it was concluded that the N_2 did not originate from the cochlear nucleus. The N_1-latency remained constant after ablation of afferent and efferent innervation, while a marked change occurred in the shape of the recorded response.
A slow negative potential directly after onset of the N_1 was found, which displaced the foot on the N_2. Recordings from the central nerve ending showed an increase in N_1-amplitude after transection of the nerve. These findings were attributed to a change in the inhibitory influence of the efferent nerve fibers on the cochlea.
In a similar experiment recordings from single auditory units at the peripheral stump of the transected eighth nerve showed no change in the spontaneous activity. The adaptation pattern to a toneburst at the characteristic frequency also remained

constant after transection of the nerve (Kiang and Sachs, 1965). The findings of Fisch and Ruben were confirmed by Daigneault and his co-workers (1968, 1970, 1974). Total disruption of all nerve fibers at the internal auditory meatus, leaving the blood supply intact, resulted in a charactertistic N_{1-2} cleft distortion of the recorded response. The altered response returned towards normal in about two hours and therefore should be regarded as an 'injury type' of response. Similar observations were made after application of local anaesthetics, which produced an altered response for the duration of action of these agents.
Various concepts have been developed to explain the characteristics of the recorded response and the changes that can occur during ischaemia of the cochlea, drug administration and nerve section, but no satisfactory explanation has been found (Boelen, 1976).
To explain the findings after eighth nerve section, suggestions have been made towards the influence of efferent innervation and various studies have been made towards the role of efferent innervation on the character of the recorded response. As has been shown by Rasmussen the efferent nerve fibers run along the vestibular nerve, which allows the production of stepwise lesions of efferent (vestibular) and afferent (cochlear) nerves. Through selective lesions the contributions to the effect of whole nerve section on the recorded response, as observed by Fisch and Ruben, can be evaluated. The first studies of selective transection and recording the various cochlear potentials were started by Daigneault (1970, 1974).
By means of vestibular nerve section the cochlea is disrupted of cochlear and vestibular efferent innervation (Spoendlin, 1963). The effect on the cochlear response is remarkable (Daigneault, 1970).

The N_1-amplitude was found to be increased after disruption of the efferent fibers. The shape of the response showed the typical N_1-N_2 cleft distortion with a complete loss of the positive peak P_1 (Daigneault, 1974). No definite influence of efferent nerve section could be shown on the N_1-latency. The effect of vestibular nerve section on the non-neural potentials CM and SP was not studied. Selective section of only the afferent nerve fibers showed only a minor towards the characteristic N_1-N_2 cleft distortion. No significant reduction in N_1-amplitude was found.
From their studies on selective nerve section Daigneault and his co-workers concluded that the observed effects could not be explained by an increased discharge in the efferent nerve fibers, since electrical stimulation of efferent nerve fibers had shown to produce an N_1-amplitude reduction (Galambos, 1956). These findings are explained on an change in tonicity of the efferent nerve fibers. However, it would seem very likely, as already suggested by Fisch and Ruben, that disruption of efferent inhibitory nerve fibers, would indeed result in an increased N_1-amplitude, as is found in the present study.
Rossi et al. (1964) studied the effect of selective section of the COCB and UOCB on the cochlear microphonics (CM).
The COCB was resected by a 2 mm downward surface incision on the sulcus medianus on the floor of the fourth ventricle at the level of the facial colliculus. Both COCB and UOCB were transected by an incision at the same level but now 1 mm lateral of the sulcus medianus. To evaluate the effects of crossed and uncrossed effe-

rent fibers on the CM, in the same animal these incisions were subsequently made after the effect on the CM was studied.
It was found that disruption of efferent innervation resulted in a reduction of the CM-amplitude and a greater reduction was found by resection of the UOCB (Rossi et al., 1964). Since the UOCB consists of a much smaller amount of nerve fibers this observation is quite remarkable. Therefore the authors emphasize the importance of another component of direct cochlear fibers, which arises in cells of the reticular formation of the medulla (Rossi and Cortensina, 1963a, 1963b).

4.2.2 Behavioral studies

Most of the work on transection experiments of efferent nerve fibers has been done with behavioral audiometry.
Unfortunately it is impossible to draw any definite conclusions from these experiments, for not only the recording and stimulation techniques are different, but also the results are sometimes conflicting. Geller and Galambos (1962) transected the COCB in two cats and found no change in behavioral thresholds. In monkeys Dewson (1968) found that the ability to discriminate stimuli in the presence of noise was impaired after transection of the COCB. This observation was confirmed in squirrel monkeys by Capps and Ades (1968), who reported a deficit in frequency discrimination performance after surgical interruption of the crossed olivocochlear bundle.
Trahiotis and Elliott (1970) made opposite observations in cats that showed a slightly increased masking effect at 1 and 2 kHz, and no influence on the threshold.
Extensive experimental work in behavioral auditory research in cats on COCB transection has been done (Igarashi, 1972, 1974, 1977).
Pure tone thresholds and test-performance as a function of signal-to-noise ratio were not influenced by COCB-section. In another study (1974) these investigators demonstrated that white noise had to be increased after COCB-section to perform a certain test. In their recent report (1977), using a visual auditory dual model, no effect of COCB-section could be demonstrated, but this negative finding might be partially explained by side-effects (ataxia). The investigators also suggest that the failure to demonstrate any influence of COCB-section might be explained on basis of a different anatomy from that described by Rasmussen and refer to the results of the horse radish peroxidase technique of Warr (1975).

4.3 Electrical stimulation

A reduction of the AP-amplitude in response to clicks was found after and during the application of trains of repetitive electrical stimuli to the crossed olivocochlear bundle on the floor of the IVth ventricle (Galambos, 1956). This N_1-amplitude reduction during electrical stimulation of the COCB has been confirmed by many others in various experimental animals (Fex, 1959; Desmedt, 1962; Sohmer, 1965; Wiederhold, 1963). The effect of stimulating the COCB appeared to be six times stronger than stimulation of the uncrossed efferents (Sohmer, 1966). The amplitude reduction of the AP was accompagnied by an increase in N_1-latency (Dayal, 1968; Daigneault, 1970; Klinke and Galley, 1974) an effect which was not found by Nieder (1970). Stimulation of the UOCB, giving a smaller amplitude reduction, did not result in a measurable change in N_1-latency (Sohmer, 1966).
The cochlear microphonics increased during electrical stimulation (Fex, 1959; Desmedt and Monaco, 1961, Wiederhold and Peake, 1966). Stimulating the COCB resulted in a decrease of the AVE SP^+ evoked by high frequency stimulation (7-12 kHz) and also a decrease in the AVE SP^- as evoked by lower frequency stimulation (Gans, 1977) while the CM appeared to increase under these conditions.
No special attention has been given to the AP-waveform, but a characteristic broadening of the response can be seen in some recordings (Wiederhold, 1966).
The maximal reduction of afferent auditory activity in single fibers in cat is found at the characteristic frequency and appeared to be optimal in the frequency range between 6 and 10 kHz (Wiederhold and Kiang, 1970; Wiederhold, 1970). Using the differential electrode recording technique Teas and Konishi (1970) came to the same conclusion for the guinea pig, the optimal effect is meassured in the 7-10 kHz range. The larger effectiveness of COCB amplitude reduction in this response area is explained on the pattern of efferent innervation along the guinea pig cochlea (Kimura and Wersäll, 1962). From their work it was also demonstrated that a CM-increment as produced by COCB stimulation depended not only on the location in the guinea pig cochlea, but also on the frequency. Above 5 kHz in turn I and above 700 Hz in turn II no CM increment did occur. For the lateral line organ of the butbot (lota lota) Flock et al. (1973) could confirm the effects of efferent stimulation in CM as well as afferent nerve impulse activity.
In recording efferent activity near the vestibulo-cochlear anastomosis it appeared that efferent fibers from the contralateral superior olive (i.e. from the COCB) were activated by afferent activity from the cochlea on that side (Fex, 1962, 1963). Pfalz (1962/1963) confirmed these findings.
The results of electrical stimulation of the olivocochlear bundle on the various cochlear potentials are summarized in Table II .

Table II: Effects of electrical stimulation of the crossed olivocochlear bundle on the various cochlear potentials.

N_1-amplitude	decreased
N_1-latency	increased
AP-waveform	broadened
Summating potential	decreased
Cochlear Microphonics	increased

4.4 Pharmacological Experiments

Acetylcholine (ACh) most likely is the transmitter substance at the efferent nerve endings. Intra-arterially applied ACh showed the expected N_1-amplitude reduction, but no influence on the CM could be demonstrated (Daigneault, 1966, Daigneault and Brown, 1970).
Since every transmitter substance acts by changing the ionpermeability at the postsynaptic membrane, Desmedt and Robertson (1973) investigated the ion-

mechanisms of efferent olivocochlear inhibition by perfusing the cat's cochlea with various ion-solution. It was found that the inhibitory transmitter (ACh?) released by COCB electrical stimulation elicits an increased conductance to small anions in the membrane of the auditory dendrite and of the outer hair cells. The inhibitory mechanism on the afferent auditory-input is primarily a post-synaptic mechanism. The effect of COCB efferent stimulation could be abolished by perfusion of strychine-nitrate solution.

4.5 Functional Significance

Although the reviewed literature about the experimental studies on the efferent nerve system has taught a great deal about efferent innervation of the cochlea, the functional significance is still unknown.
Any suggestion about the role of efferent innervation in the mechanism of hearing has been purely theoretical. Its persistence in the course of evolution of the various species, and the presence in man, is no proof of any functional significance (Klinke and Galley, 1974). In their extensive review about vestibular and cochlear efferents these authors quote House and Fisch in saying that vestibular nerve section in patients with Menière disease, would make the ear more 'sensitive to high intensity noise'. This observation can also be explained by the recruitment phenomena in these patients.
A possible role of efferent nerve fibers has been attributed toward a centripetal part of a feedback loop (Fex, 1962). Several objections have been made against the idea of a simple feedback loop. The long latency would make the functional significance as a simple feedback loop unlikely. It was also found that sound stimuli are not capable of causing any adequate efferent discharge (Pfalz, 1969). Other suggestions about the physiological significance of efferent innervation dealt with effects of peripheral auditory adaptation. Various studies failed, however, to provide such evidence (Kiang, 1965, Dayal, 1970, Daigneault, 1970).

V Design and motivation of the experiments

In reviewing the surgical treatment of acoustic neurinomas the importance of diagnosis at an early stage has been stressed. Small tumors can be removed either by the middle fossa approach or translabyrinthine technique. The interested E.N.T.-physician has not only become closely involved with surgical treatment of these tumors, he also has advanced tools to come to an early diagnosis. In these days high frequency loss, with absent Stapediusreflex or abnormal reflex decay and labyrinth dysfunction are considered early symptoms of an acoustic neurinoma, instead of papilledema and facial weakness, as in the old days. It is also of great importance that early diagnosis and accurate treatment can not only prevent the serious risks of facial nerve injury and bleeding in the posterior fossa, but also offers the possibility to restore eighth nerve function. *What can electrocochleography and the recording of brainstem responses offer for an early diagnosis of small acoustic tumor?* Recent studies with these techniques have indeed shown that there are characteristic findings in retrocochlear pathology (Beagley, 1974, Selters and Brackmann, 1977, Odenthal and Eggermont, 1976). *The problem is, however, that it is not yet known, how these characteristic findings should be interpreted.*
First of all more should be known about the cause of the characteristic changes in the electrocochlear recordings from the cochlea and eighth nerve in retrocochlear pathology. This study is an effort to produce experimental retrocochlear lesions in guinea pig, that mimic the effects of acoustic neurinomas, in order to produce an experimental model of acoustic neurinoma.
By producing subsequent experimental effects an effort is made to interpret the characteristic findings in retrocochlear pathology in man.
The guinea pig is a suitable animal for experiments on retrocochlear lesions. The favorable anatomical situation is present, in which vestibular and cochlear nerve run a separate course. This enables selective experiments on either of these nerves. In most cases the origin of an acoustic neurinoma is the vestibular nerve, so selective experiments on this nerve are of special interest. It is known that acoustic neurinomas tend to grow by direct volume expansion, exerting pressure and stretch on the surrounding structures. *To mimic these effects a technique was designed to apply selective stretch on either the vestibular or cochlear nerve.* The placement of a silicone balloon (Chinn and Miller, 1975), had to be disregarded since the balloon would exert pressure on both nerves. In this study a middle ear surgery instrument (stapes hook) was gently placed underneath the vestibular or cochlear nerve, which was then lifted up for about 1 mm rostrally during 1-2 seconds.
Care was taken not to interfere with the cochlear blood supply, especially in experiments on the cochlear nerve, since the main artery runs along the cochlear nerve.

Any quantitative method of applying stretch would at least require the introduction of a balloon or a string around the nerve, which would certainly interfere with the recordings. Further expansion of an acoustic neurinoma may eventually completely compress the eighth nerve and block nerve fiber transmission. Complete loss of nerve function was simulated by selective transection of the nerve.
These possible effects of acoustic tumors were originally studied in experiments involving selective stretch and section of vestibular and cochlear nerves. *Earlier work on nerve section had already suggested a possible influence of efferent innervation. Therefore the experiments were especially extented towards the influence of efferent innervation.* This observation is of special interest since most acoustic neurinomas originate from the vestibular nerve, while the efferent innervation passes along the vestibular nerve in guinea pig and in man along the vestibular branch of the eighth nerve (Gacek, 1961, 1974).
Experiments on selective stretch of the vestibular nerve were combined with or preceeded by transection of crossed efferent fibers in order to study the separate influence of uncrossed and crossed efferent fibers. Local application of KCl to induce a block in nerve fiber transmission was done, optionally with intravenously administration of strychnine. Because of the crossed course of the efferent nerve fibers and a possible feedback influence experiments with bilateral recording were also carried out.
The results were evaluated against well-known hearing models in order to find an explanation for the results found in retrocochlear lesions as presented in this study. With the obtained experimental data an effort was made to interpret the results of clinical electrocochleography in retrocochlear pathology.

VI Methods

6.1 Introduction

Electrocochleography is the recording of stimulans related potentials generated in the cochlea and the first order neurons forming the auditory nerve (Eggermont, 1976 a).
The potentials can be recorded from various sites: transtympanic from the promontory, or as in the present study, from the round window. The recorded potentials are the cochlear microphonics (CM), the summating potential (SP) and the compound action potential (AP). These potentials can be evoked by either so called wide or narrow band stimuli. The click stimulus provides the best synchronization of the single nerve fiber firings but contains a large number of frequencies. A limitation therefore is that no frequency specificity can be obtained. In the present experiment besides click, mostly short tonebursts were used. These toneburst stimuli have two periods of a sinewave during the rise and fall time and at least six periods during the plateau (Eggermont, 1976 b).

A detailed description of the technical data of the ECoG-apparatus as used in the present experiment is given by Spoor (1974). In principle the equipment consists of two main parts; a stimulation and a recording system. The stimulating part consists of a stimulus generating and a stimulus transducing system. The recording part is formed by a preamplifier and a main amplifier and also includes an oscilloscope. An electronic averager is used to enhance the relevant signal from background noise. In the present study tone bursts generated at various frequencies, 2 kHz, 3 kHz, 4 kHz and 6 kHz were used. The responses were mostly recorded from the round window menbrane, using a silver wire electrode.
In several animals brainstem responses were recorded by an electrode placed on the dura vertex.
In several experiments the olivo-cochlear bundle on the floor of the fourth ventricle was electrically stimulated with a bipolar electrode (300 impulses/sec., 4-8 Volt).

6.1.1 Narrow-band AP-responses

In various experiments so called narrow-band AP-responses (NAP) have been recorded.
This narrow-band AP-responses is a synchronous firing of a limited number of nerve fibers innervating a narrow region of the cochlear partition.
By separation the compound AP into NAP's it is possible to investigate relatively

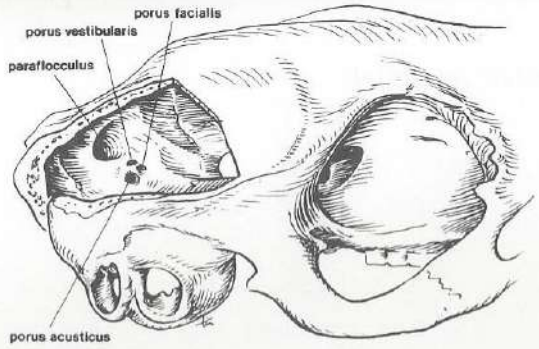
small areas on the cochlear partition (3 mm). The NAP's can be derived by the use of a high-pass noise masking (Teas et al. 1962, Eggermont 1976 b).

6.1.2 The technique of deriving narrow-band AP's

In the present study tone-bursts at 3 kHz were used but every stimulus capable of evoking AP's is useful. At 80 dB SPL the whole nerve response AP_∞ was first recorded and stored in the computer memory. Then the level of wide band noise was determined, that will just mask the compound AP (AO_∞) which is mostly 5 dB less. Without any further changes in the level of the wide band masking the high pass cut-off frequency is increased from 0 to 10 kHz wide band noise, and the resulting AP_{10} is recorded. The AP_{10} is the response of the entire cochlea to the tone burst minus that part masked by the 10 kHz high-pass noise. The next cut-off frequency (e.g. 8 kHz) is then used and the AP_8 is recorded.
Subtraction of the AP_8 from the AP_{10} gives the narrow-band at the part of the cochlea masked by the 8 kHz high-pass noise but not by the 10 kHz high-pass noise. In this way a compound AP response to a tone burst can be separated in several NAP's.

6.2 The Surgical approach to the Cerebellopontine Angle in Guinea Pigs

In this study 68 healthy guinea pigs were used. Anaesthesia was accomplished by intraperitoneally injected Urethane® in a 20% watery solution. Dosis of 1.0 - 1.5 ml/100 gr. were administrated, increasing with the animal weight. After a routine tracheotomy the experimental animal was placed into a standard stereotaxis apparatus.
The rectal temperature was continuously monitored and kept constant at 38°C.
A midline skin incision was made over the skull, which was extended bilaterally into a retro-auricular incision. The skin flaps were sutured in a fixed position. Part of the parietal skull and the complete occipital bone up to the nuchal crest were exposed. Over a short distance the neck muscles were removed. The cerebellopontine angle in guinea pig can be approached by partial removal of the occipital and parietal bone. The dura is then opened and care is taken not to severe the sagital sinus. Posteriorly the cerebellopontine angle is boarded by the lobulus para-flocculus of the cerebellum. Part of the cerebellum and the lobus para-flocculus are gently sucked away. An adequate posterior view is now obtained within the cerebello-pontine angle. (See illustration.)
This operation procedure does not influence the round window recorded parameters (SP, CM, AP).
The vestibular nerve can be identified. The vestibular division of the eighth nerve runs a separate course from the cochlear nerve. With respect to the bony excavation of the para-flocculus the internal meatus of the vestibular nerve is located anteriorly and slightly inferiorly. The internal acoustic meatus is located posteriorly and inferiorly to this bony excavation. By careful manipulation the vestibular nerve can easily be exposed from the brainstem to the internal vestibular meatus, without interference with the cochlear nerve. There are no blood vessels of any functional importance



that pass along the vestibular nerve, and transection of the nerve does not interfere with the cochlear blood supply. The surgical anatomy is illustrated here. Exposure of the cochlear nerve without interference with the vestibular nerve acquires a different approach. By gently lifting up the cerebellum the posterior cranial fossa is entered and the cochlear nerve exposed by a sub occipital approach. Care should be taken not to interfere with the cochlear blood supply.
The main artery to the cochlea runs along the cochlear division of the eighth nerve. Any arterial bleeding in this area results in a rapid loss of cochlear potentials. In the present study the facial nerve was not routinely identified. The internal facial meatus projects slightly inferior and cranial to the vestibular meatus. The facial nerve can be exposed by a more cranial approach to the cerebellopontine angle, by gently holding the tempero parietal lobe aside. However, care should be taken not to excert any stretch on the vestibular nerve. By suction away the mid portion of the cerebellum the fourth centricle is exposed and the genu of the facial nerve can be identified. The olivo cochlear bundles decussate in the midline just rostral of the facial genu on the floor of the fourth ventricle.
Using a fine stapes hook the vestibular nerve could either be stretched by moving the stapes hook about 1 mm upward during 1 to 2 seconds, or the nerve was transected using a micro-knife.
Initially the 'midline fossa approach' to the cerebellopontine angle was used, but no suitable technique was found to retract the cerebrum far enough for a good exposure without the danger of applying stretch to the nerve structures.
Later on the suboccipital approach was standardly used.
The round window was visualized by a small drill hole into the bulla tympanica. A silver wire electrode was placed under direct vision and fixed with dental cement. All animals were routinely screened by their ear reflex on a sharp standard click, since in case of an upper respiratory tract infection visualization of the round window was impossible, because of the presence of glue material in the middle ear.
In most animals standard recordings were made before exposing the eighth nerve structures, and it was controlled that this procudure did not affect the standard recordings. In some animals the crossed olivo-cochlear bundle was stimulated on the floor of the fourth ventricle. The fourth ventricle was exposed by gentle section of the cerebellum overlying the IVth ventricle with the aid of a micromanipulator. A bipolar stimulation electrode was placed just rostral to the genus of the facial nerve. In case of COCB-transection, an incision was made on the sulcus medianus about 2-3 mm long, 1 mm deep and the same level.

Introduction

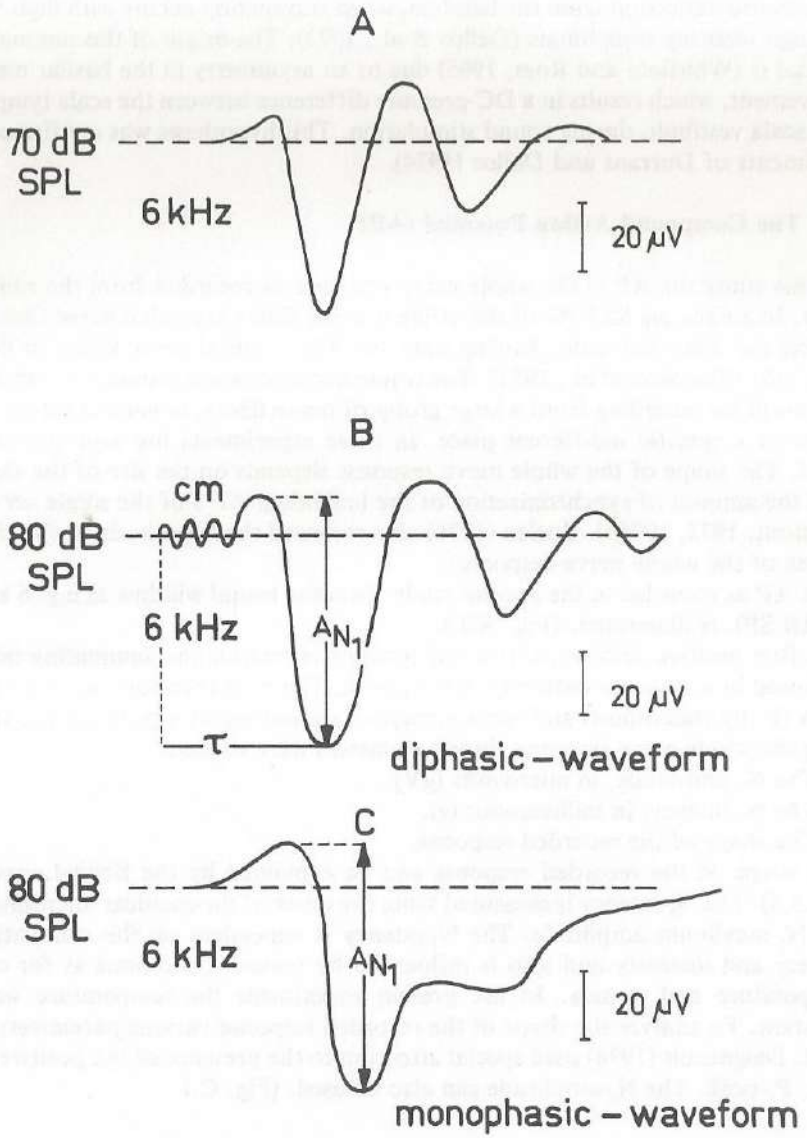
In the present thesis three potentials are recorded from the round window
1. The cochlear microphonics (CM).
2. The summating potential (SP).
3. The compound action potental (AP).
The characteristics of these potentials will be briefly reviewed.

7.1 The Cochlear Microphonics

The cochlear microphonics (CM) is a receptor potential, that can be recorded from almost anywhere in the cochlea or from the cochlea surface. This potential was first demonstrated by Wever and Bray in 1930. The CM can also be recorded from the round window as was done in this study. A limitation of this recording site is, however, that an overall gross response is recorded as a weighted average over the individual hair cells.
Furthermore only information is obtained from the upper basal turn of the cochlea. These difficulties in evaluating the CM from the round window might partially explain the sometimes confusing findings in CM-recording in electrocochleography (Teas et al., 1972, Whitfield and Ross, 1965).
Tasaki and Fernandez (1952) have demonstrated that with intracochlear differential electrodes CM-recordings from various discrete positions within the cochlea can be done. The recorded signal is however not representative for the output waveform of a given individual hair cell as has been emphasized by Whitfield and Ross (1965). In experimental studies on the CM the intracochlear differential electrode technique is mostly used (Teas, 1970).
Von Békésy (1960) has demonstrated that in the normal cochlea the CM is proportional to the displacement of the basilar membrane. Since the CM, being a receptor potential, is generated, on the hair-surfase of the haircells, these potentials provide information about the validity of the hair cells in the cochlea. Experiments with ototoxic drugs (Dallos et al., 1972, Stange, 1970) suggest that the cochlear microphonics are generated mainly by the outer hair cells.

7.2 The Summating Potential

A second stimulus-related hair-cell potential was found to be generated near the cuticular lamina of the hair cells and is called the summating potential (SP). It was described by Davis et al. (1958) and Tasaki (1954).



The SP appears as a D.C. shift of the baseline, and may be positive or negative, with respect to the scala media. For a positive summating potential the scala media is relatively positive with respect to the scala tympani.
Under various experimental conditions, e.g. anoxia, electric polarization-differences between scala tympani and vestibuli, and certain drugs (furosemide) the SP polarity may change.
From round window recordings in the guinea pig one nearly always finds the SP as

an upward deflection from the baseline, when stimulation occurs with high frequency high intensity tone bursts (Dallos et al., 1972). The origin of the summating potential is (Whitfield and Ross, 1965) due to an asymmetry in the basilar membrane movement, which results in a DC-pressure difference between the scala tympani and the scala vestibuli, during sound stimulation. This hypothesis was confirmed by experiments of Durrant and Dallos (1974).

7.3 The Compound Action Potential (AP)

In this study the AP is the whole nerve response as recorded from the round window. In guinea pig 85-90% of the afferent nerve fibers are radial nerve fibers innervating the inner hair cells, leaving only 10-15% of spiral nerve fibers to the outer hair cells (Morisson et al., 1975). The whole nerve response is based on simulaneous extracellular recording from a large group of nerve fibers, towards a reference electrode at a specific indifferent place. In these experiments the neck muscles were used. The shape of the whole nerve response depends on the site of the electrodes and the amount of synchronization of the individual AP's of the single nerves (Eggermont, 1972, 1976b). Boelen (1976) also reviewed the hypothesis on the characteristics of the whole nerve response.
This AP as recorded in the present study from the round window at e.g. 6 kHz and 70 dB SPL is illustrated. (Fig. AB.)
The first positive deflection from the baseline represents the summating potential, followed by a negative deflection the N_1 peak. The N_1 is then followed by a positive peak (P_1 by Daigneault) and subsequentyly a second negative peak the N_2. In recording the whole nerve response three parameters were studied:
1. The N_1-amplitude, in microvolts (μV).
2. The N_1-latency, in milliseconds (τ).
3. The shape of the recorded response.

The shape of the recorded response can be explained by the Keith-Lucas model (XI.5.3). The N_1-latency is measured from the onset of the cochlear microphonics to the N_1-maximum amplitude. The N_1-latency is dependent on the stimulation frequency and intensity and also is influenced by various conditions as for example temperature and anoxia. In the present experiment the temperature was kept constant. To analyze the shape of the recorded response various parameters can be used. Daigneault (1974) paid special attention to the presence of the positive deflection, P_1-peak. The N_2-amplitude can also be used. (Fig. C.)

VIII Experimental Results I

8.1 Introduction

This section will deal with experiments that are intended to mimic the effects produced by a tumor process in the cerebropontine angle. The separate course of the vestibular and cochlear nerves in the guinea pig internal auditory meatus allows selective effects to be produced on each nerve. First of all the results of applying selective stretch or transection of the vestibular or the cochlear nerve are described. In case of the cochlear nerve no attempt was made to achieve a complete transection in order not to interfere with the cochlear blood supply. The effects are studied with respect to changes in
1. the N_1 amplitude,
2. the N_1 latency,
3. the waveform of the compound AP,
4. the amplitude of the summating potential,
5. the amplitude of the cochlear microphinics.

- *The lesions in the various experiments are shown in figure 57.*

8.2 Transection of the vestibular nerve

In 11 animals the vestibular nerve was selectively transected at the internal meatus. As toneburst frequencies 2 and 6 kHz are used. Results are generally presented as a plot of all individual experiments and further on elucidated by a typical example.

8.2.1 The N_1-amplitude

The ratio of the N_1 amplitudes after ($A^*_{N_1}$) and before (A_{N_1}) vestibular nerve transection is plotted for all animals at 40, 60 and 80 dB SPL (Figure 1). The statistical tests are based on the one sided Student test for the means. Except at 40 dB, 6 kHz there is no significant difference ($p > 0.01$) from a value of 1 (no change). An individual experiment illustrates this (Figs 2 and 3). The A_{N_1} is plotted on a logarithmic scale against intensity in dB. At 2 kHz there is hardly any change (Fig. 2), while for 6 kHz (Fig 3) there is a definite increase of A_{N_1} at low intensity levels leading to a threshold decrease, this appears to be a transient effect since complete recovery to the initial situation is obtained 2 hours after transection. This type of effect is therefore not likely to be of importance for explaining the effect of tumors.
Of some more importance is the compound AP waveform; (see insert) transection

has a clear effect, at 2 kHz the individual N_1, N_2, N_3 type of response appears to be a broadly fused AP after transection. In the 6 kHz series one notices a disappearing of the P_1-peak.

8.2.2 The N_1-latency

The latency difference before and after transection is plotted in Fig 4 for 40, 60 and 80 dB SPL and 2 and 6 kHz toneburst stimulation. There appears to be hardly any systematic change in latency, the mean changes are +0.12; +0.08 and +0.06 msec i.e. in general a latency increase. This increase is, however, not significantly different from zero ($p > 0.01$).

8.2.3 The waveform of the compound AP

The compound AP waveforms shown in the inserts of Figs 2 and 3 demonstrate the changes which occur immediately after transection. The normal response at e.g. 6 kHz can be described as starting with a positive deflection (SP^+), followed by a negative (N_1) – positive (P_1) – negative (N_2) potential constituting the AP. After transection the P_1 is lost and the response as a whole changes to a broad rather indifferent wave ('N_1-N_2 cleft distortion', Ruben, 1962).
Using masking with high-pass filtered noise one may derive narrow-band AP waveforms (NAP) assumed to be the synchronous response from ½ octave wide regions on the cochlear partition (Section VII 4.). For a 3 kHz toneburst (70 dB SPL) the analysis is shown in Fig 5 for three particular NAP's before and after transection. One notes that the cleft distortion is already apparent in the NAP's indicating that probably the waveform of the unit contribution is changed. Plotting the NAP amplitudes against the central frequency of the various narrow-bands (Fig 6) shows that there is a definite change only in the 5-7 kHz area. The latencies of the NAP's show some minor increase.

8.2.4 The summating potential and cochlear microphonics

The summating potential generally is not very clear in case of 2 kHz stimulation therefore the results reported are restricted to 6 kHz. A review of the ratio of the SP after and before transection at 90 and 100 dB SPL is shown in Fig 7. The values scatter around 1 showing an average of 0.95 being not significantly different from 1. ($p > 0.01$).
A somewhat extended view of the effects on SP is shown in Fig 8 giving SP input-output curves in three animals before and after transection, no definite changes occur.
The cochlear microphonics have been recorded in only one experiment, no change was found.

The effects are summarized in Table III

Table III: Effect of transection of the vestibular nerve on the AP, SP and CM

N_1-amplitude	: no change
N_1-latency	: no change
AP-waveform	: monophasic*
SP-amplitude	: no change
CM-amplitude	: no change

8.3 Selective stretch of the vestibular nerve

In 24 animals selective stretch was applied by gently lifting the vestibular nerve with a stapes-hook placed underneath the nerve. Special care was taken not to touch the cochlear nerve to prevent any directly applied stretch or pressure thereupon. The surgical approach allowed a good view of the vestibular nerve.

8.3.1 The N_1-amplitude

In contrast to the effects of transection, minimal stretch of the vestibular nerve resulted in a marked effect on the N_1-amplitude. In some animals even minimal contact between the stapes-hook and the nerve resulted already in an change of N_1.
The ratio of $A^*_{N_1}$ (after) and A_{N_1} (before) is plotted for 40,60 and 80 dB SPL at 6 kHz the average values are respectively 0.48; 0.57 and 0.60 being all significantly different from 1 ($p > 0.01$) but not different in between ($p > 0.01$) (Fig 9).
An individual experiment (Fig 10) shows the N_1-amplitude reduction and also that 60 minutes later a further reduction of the AP-amplitude at 70, 80, 90 and 100 dB SPL has occurred (Fig 10).

8.3.2 N_1-latency

The decrease in N_1-amplitude was accompagnied by an increase in N_1-latency (Fig 11) which at 40, 60 and 80 dB SPL (6 kHz) was on the average 0.19; 0.16 and 0.13 msec and proved to be significantly different from zero ($p > 0.01$). The small latency increase in an individual animal is also shown in Fig 10. It must be remarked that the general trend is that the more the amplitude decreases, the larger is the latency increase for these experiments.

8.3.3 The waveform of the compound AP

As was the case for transection of the vestibular nerve, stretch caused the waveform of the AP to loose its definite N_1, N_2 type (Fig 10). A narrow-band analysis shows this very clearly (Fig 12). The narrow-band amplitudes drop over the whole frequency range but more strongly at the lower central frequencies, at all CF's a slight reduction in the NAP-latencies was found (Fig 13).

8.3.4 The summating potential and cochlear microphonics

In general the SP decreased just as the AP as a result of stretch, the SP ratio decreased at 90 dB SPL (6 kHz) on the average to 0.58 and at 100 dB to 0.60 (Fig 14). The CM amplitude nicely paralleled this showing a change by a factor of 0.41 at 80 dB and by 0.52 at 90 dB. All these values are significant different from 1 ($p > 0.01$).

The effects of stretch are summarized in Table IV

Table IV: Effect of stretch on the vestibular nerve upon the AP, SP and CM

N_1-amplitude	: decreased*
N_1-latency	: increased*
AP-waveform	: monophasic*
Summating potential	: decreased*
cochlear microphonics	: decreased*

8.4 Partial transection of the cochlear nerve

Transection of the cochlear nerve present some delicate problems. The approach to this part of the eight nerve has to be by a suboccipital technique in order not to interfere with the vestibular nerve. Even minor stretch of the vestibular nerve greatly influences the characteristics of the recorded response (previous section). In addition any interference with the cochlear blood supply should be avoided while a main cochlear artery runs along the cochlear nerve. Efforts have been made for a complete cochlear nerve transection without severing the cochlear blood supply. All attempts, however, invariably resulted in a rapid loss of the recorded responses. Therefore, the results that will be presented here deal only with partial transection of the cochlear nerve.

8.4.1 The N_1-amplitude

In 8 animals the effect of transection has been studied at 2 and/or 6 kHz toneburst stimulation at 60, 80 and 100 dB SPL. The $A^*_{N_1}$ (after) to A_{N_1} (before) ratio for 6 kHz on the average shows a decrease being respectively 0.65; 0.54; 0.43 and significantly different from 1 ($p > 0.01$). This is shown in Fig 15. At 2 kHz the decrease is respectively to 0.80; 0.74; 0.60 being not significantly different from 1 at 60 dB SPL. An individual example shows the more pronounced decrease occurring at the higher intensities (Fig 16).

8.4.2 The N_1-latency

The effect of partial transection on the N_1-latency is not that clear, on the average there is a decrease of 0.08 msec; 0.10; 0.13 msec respectively at 60, 80 and 100 dB SPL at 6 kHz and an increase of 0.20; 0.22; 0.18 msec at the same intensities at 2 kHz. The decrease, resp. increase is significantly different from zero only at the highest intensity (Fig 17).

8.4.3 The waveform of the compound AP

As Fig 18 shows, transection of the cochlear nerve produced the same change in the waveform of the AP as did manipulation of the vestibular nerve. A more quantitative analysis (Fig 19) of the narrow-band AP waveforms shows the same effect, the NAP amplitudes decrease mainly at the higher central frequencies, thereby backing the findings in the compound AP which showed no significant change for the 2 kHz stimulation at lower intensities.

8.4.4 The summating potential and cochlear microphonics

After partial transection of the cochlear nerve the SP was found to be reduced on the average to 0.56 times the value before transection (100 dB SPL, 6 kHz). In general there was only minimal reduction, in two cases there was a nearly complete loss of SP, accompagnied also by a very large reduction in the AP. Therefore in these two cases an interference with the cochlear blood might have occured.
Input-output curves for more typical animals are shown in Fig 20 showing a moderate decrease in the SP over the whole intensity range.

The effects of partial transection of the cochlear nerve are summarized in Table V.

Table V: Effects of partial transection of the cochlear nerve in AP en SP

N_1-amplitude	: decreased*
N_1-latency	: decreased (6 kHz), increased (2 kHz)*
AP-waveform	: monophasic*
Summating potential	: decreased*

8.5 Selective stretch of the cochlear nerve

In 5 animals selective stretch of the cochlear nerve was performed using the same technique as for the vestibular nerve.
The results of preceeding sections have shown that minimal interference with the vestibular nerve had marked influence on the AP-parameters. To rule out a direct mechanical influence upon the vestibular nerve during stretch of the cochlear nerve the vestibular nerve was transected first in two experiments and then stretch was applied to the cochlear nerve. The results thereof will be presented here.

8.5.1 The N_1-amplitude

In general the A_{N_1} increases after stretch applied to the cochlear nerve in striking contrast to the effect produced by stretching the vestibular nerve. In Fig 21 results are shown at 2 and 6 kHz stimulation at 60 and 80 dB SPL. For two individual animals input-output curves are shown for the normal situation and after stretching of the auditory nerve. In one experiment selective stretch is applied to the cochlear nerve (Fig 22). In the second experiment stretch of the cochlear nerve is applied after

transection of the vestibular nerve (Fig 23). In both situations there is an increase in amplitude especially at the lower intensities.
A series of experiments for 2 kHz 70 dB SPL stimulation shows the amplitude changes after stretch and section of the vestibular nerve and subsequent stretch on the cochlear nerve (Fig 24) which shows invariably an amplitude increase relative to the value just before stretch was applied.

8.5.2 The N_1-latency

The effects of cochlear nerve stretch on the N_1-latency is variable. At high intensities for 2 kHz stimulation there is a latency increase (0.11 msec), (Fig 25) while for lower intensities the 6 kHz produces a slight latency decrease (0.08 msec, 60 dB).

8.5.3 The waveform of the compound AP

As nearly all manipulation in the internal meatus, stretch applied to the cochlear nerve also resulted in a change of the AP towards a more monophasic waveform (Fig 26).
This is also clear in the NAP-waveform. As Fig 27 shows stretch of the cochlear nerve, after transection of the vestibular nerve, shows an increase for all NAP-amplitudes, there appears to be no specific frequency-effect.

8.5.4 The summating potential and cochlear microphonics

The SP on the average showed a slight increase after stretching the cochlear nerve, at 100 dB, 6 kHz an average ratio of 1.16 being found being significantly different from 1 ($p > 0.01$). No recordings of the cochlear microphonics have been made. (Fig 28).

8.5.5 Combination of all effects

For the results presented here an overall review is presented in Table VI. An asterix indicates a significant change.

Table VII: Effects of manipulation in the internal auditory meatus on AP, SP and CM

parameter	vestibular nerve		cochlear nerve	
	transection	stretch	transection	stretch
N_1-amplitude	no change	decrease*	decrease*	increase*
N_1-latency	no change	increase*	decrease* (6 kHz) increase* (2 kHz)	decrease* (6 kHz) increase* 2 kHz)
AP-waveform	monophasic*	monophasic*	monophasic*	monophasic*
AP-amplitude	no change	decrease*	decrease*	increase*
CM-amplitude	no change	decrease*	—	—

The general conclusion is that the AP-waveform is consistently changed from an N_1, N_2 type of response with a distinct positive peak in between, towards a broad monophasic type of response. The other effects are not consistent for each type of interference to that in real situation (tumors of the vestibular nerve) it is likely these effects could balance or at least could partially compensate each other.

8.6 Contralateral effects of stretch on the vestibular nerve

The previous experiments have shown that manipulation in the internal meatus, even if restricted to only minor stretch of the vestibular nerve greatly affect the AP as well as the cochlear potentials. The only relation between the vestibular nerve and the cochlear potentials as well as with the auditory nerve action potential is mediated by the efferent nerve fibers. The efferent nerve system consists of crossed and uncrossed efferent fibers. The crossed fibers take their origin in the contralateral accessory olive.
It would be interesting to know if effects of selective manipulation on the ipsilateral vestibular nerve could influence the parameters recorded from the contralateral ear.

In five experiments selective stretch has been applied to the vestibular nerve and bilateral round window recordings were made. The effects are studied on the same set of parameters as used in former sections.

8.6.1 The N_1-amplitude

Selective stretch of the vestibular nerve results (section VIII 3.1) in an decrease of the homolateral A_{N_1}. The contralateral A_{N_1} did increase (Fig 29). This effect was so clear that in all these 5 experiments the ipsilateral ratio $A^*_{N_1}/A_{N_1}$ decreased while the contralateral ratio always increased.
At 40, 60, 80 dB SPL for 6 kHz the average ratio's were 0.50; 0.65 and 0.66 at the ipsilateral site, and 3.33, 1.96 and 1.63 at the contralateral site. All changes differ significantly from 1 ($p > 0.01$). A specific example is shown in Fig 30.

8.6.2 The N_1-latency

Just as in case of the N_1-amplitude the increase in latency at the ipsilateral site is accompagnied by a decrease at the contralateral site. The respective average changes at 40; 60 and 80 dB SPL are ipsilateral: $+0.24$; 0.09; 0.13, and contralateral -0.09; -0.09; -0.02. All values except the last one are significantly different from 0 ($p > 0.01$) (fig 31).

8.6.3 The waveform of the compound AP

The results of section VIII 3. are confirmed with respect to the ipsilateral site changes, while at the contralateral site no change has been observed in the waveform of the recorded responses.

8.6.4. The summating potential and cochlear microphonics

Stretch of the vestibular nerve produced an ipsilateral decrease in the SP as well as CM amplitude (cf VIII 3.4). This is confirmed in set of animals, and in addition it could be demonstrated that at the contralateral site the CM is increased while the SP increased slightly or stayed the same. While the effects on the CM are significant those on the SP are not. (Fig 32).

The effects have been summarized in Table VII

Table VII: Contralateral and Ipsilateral effects of unilateral stretch applied to the vestibular nerve

	ipsilateral	contralateral
N_1-amplitude	decrease*	increase*
N_1-latency	increase*	decrease*
AP-waveform	monophasic*	no change
Summating potential	decrease*	no change
cochlear microphonics	decrease*	increase*

8.7. Discussion

The results of the various experiments have been summarized in Tables VI and VII. These data show that the effects are consistent with respect to changes in the AP-waveform and also that a decrease in the N_1-amplitude is always accompanied by a decrease of the cochlear potentials (CM and SP). The increase of the N_1-amplitude is accompanied by an increase in CM and SP. The first observation places the effect of the experimentally induced changes to be very peripheral or on an common source (e.g. metabolism, blood supply).
On the other hand definite changes have been demonstrated at the contralateral ear, which are unlikely to be due to effects of interference with the contralateral blood supply. In addittion these effects are the opposite of what takes place at the ipsilateral ear. This suggests the involment of the crossed efferent system.
Some conclusive experiments have been performed on the influence of the crossed olivo cochlear bundle (e.g. Wiederhold and Peake, 1966, Wiederhold, 1970, Wiederhold and Kiang, 1970). With respect to click evoked whole nerve AP's there was a definite reduction in the amplitude at the lower intensities and no effect at high intensities, thereby increasing the threshold. This effect mimics the behaviour of input-output curves in e.g. recruiting ears and was much more prominent for high frequency evoked AP's than for low frequency ones. At high intensities a small increase in CM was noted too, this however was more clear at the lower frequencies. Assuming that stimulation of the crossed olivo-cochlear bundle produces an increase in mainly outer haircell current, while inner haircell produced neural activity is decreased, a selective inhibition model has been devised (Desmedt 1961, Geisler, 1974, Gans, 1977).

Thereby stimulation of the COCB produces an increase in current through the outer haircells by increased permeability of the cell membrane, therefore less current passes through the inner haircells. The effects may be summarized in Table VIII.

Table VIII: Effects of increased activity of the efferent system by the use of electrical stimulation

	auditory stimulation	
	low intensity	high intensity
N_1-amplitude	decreased*	no change
N_1-latency	increased*	no change
AP-waveform	broadened*	no change
Summating-potential	decreased*	decreased*
Cochlear microphonics	increased*	increased*

In comparing these changes to those produced by mechanical interference with the internal auditory meatus one tentatively arrives at the following conclusions:
1) except with respect to cochlear microphonics stretch of the vestibular nerve resembles the effects produced by increased efferent activity at the ipsilateral site.
2) At the contralateral site this could be paralleled by decreased efferent activity, produced by the decrease in afferent activity at the site of the nerve stretch.

The changes produced by interfering with the cochlear nerve can be explained either on the basis of slight cochlear damage (mainly to the basal turn) in case of cochlear nerve transection and/or on the basis of blocking afferent conduction at the site of the application of stretch. The 'or' situation refers to the stretch condition only, in this case the positive deflection wave, when the action current enters the brain side of the internal meatus, is missing. This changes the AP to monophasic and also causes the negative deflection to be slightly prolonged and increased which will especially fit the 2 kHz data (compare Beagley et al., 1977).
So at this point a combination of interfering with cochlear blood supply and nerve conduction block could explain the findings pertaining to stretch and transection of the cochlear nerve.
The findings produced by stretch of the vestibular nerve can be explained by either an interference with the cochlear metabolism or an increase of efferent nerve activity. Transection of the vestibular nerve seems to produce mainly a transient (1-2 hrs) effect based upon injury type increase of efferent activity. However, after these transient phenomena one would expect some increase in AP by the decrease or dying out of efferent activity.
To decide between this variety of possibilities, additional experiments involving transection of the COCB and local application of drugs are required. They will be described in the following sections.

IX Experimental Results II

9.1 Introduction

This section deals with experiments directly related to the postulated efferent interaction mediated by the fibers passing alongside the vestibular nerve. It was assumed in section VIII.7 that either stretch or transection of the vestibular nerve interfered with this efferent influence upon the cochlea. The first part of this section combines stretching of the vestibular nerve with transection of the COCB in the floor of the IVth ventricle. This transection either preceedes or follows the application of stretch. The second part of this section deals with the application, local or systemic, of certain drugs influencing the efferent nervous system.

As in the preceding Chapter the various experiments will be studied with respect to:

1. The N_1-amplitude,
2. The N_1-latency,
3. The waveform of the compound AP,
4. The amplitude of the summating potential,
5. The amplitude of the cochlear microphonics.

9.2 Selective stretch of the vestibular nerve followed by transection of the COCB

In four animals stretching of the vestibular nerve is followed by transection of the COCB (Rossi, 1964).

In two experiments recording is also done from the contralateral ear. No histological control studies on the efficacy of the transection have been done. The input-output curve for 6 kHz in an individual experiments is shown in Fig 33. The whole curve shifts to the right following stretch of the vestibular nerve (cf VIII.2); subsequent transection of the COCB has little or no effect.

For the ear contralateral to the side at which the vestibular nerve was stretched one observes the moderate amplitude increase after stretch (VIII.6) and there is just a minor change following COCB transection (Fig 34).

The N_1 ratio, before and after stretch of the vestibular nerve, and after stretch and COCB transection have been calculated (Table IX).

The N_1-amplitude ratio before and after stretching the vestibular nerve is shown in the upper row for the three intensities and is calculated for all four animals.

Thereafter the olivo-cochlear bundle is transected and the amplitude ratios (referred to the initial situation) are calculated again and shown in the lower row at each intensity.

Table IX: Illustrating the effect of selective stretch of the vestibular nerve on the AP-amplitude, followed by transection of the crossed olivo-cochlear bundle.

A_{N_1}-ratio	A	B	C	D
stretch vest. nerve 40 dB SPL	0.40	0.50	0.03	—
transection COCB	0.98	1.20	1.00	—
stretch vest. nerve 60 dB SPL	0.80	0.40	0.88	0.21
transection COCB	1.00	1.45	1.10	0.89
stretch vest. nerve 80 dB SPL	0.73	0.42	0.45	0.82
transection COCB	0.84	0.93	1.05	1.00

The average reduction at all frequencies after stretch is 0.54. The average change of COCB transection is 1.04.

The N_1-latency shows a similar pattern. On the homolateral side a slight increase after stretch and on the contralateral side a reduction (cf VIII.2.2). Transection of the COCB does not influence the latency on the homolateral side, but a slight increase towards the normal level is found on the contralateral side.

Of special interest is the effect of COCB transection upon the (by stretch of the vestibular nerve) broadened AP-waveform.

It is observed that immediately after the COCB transection the broad N_1-N_2 cleft distorted (VIII.2.3) returns to its original configuration (Fig 35).

No change is observed in the waveform of the AP at the contralateral ear neither by stretch of the vestibular nerve (cf VIII.6) and subsequent transection of the COCB.

The amplitude of the summating potential appears to be reduced after stretch of the vestibular nerve (VIII.2.4) and tends to increase again after transection of the COCB (Fig 36), at least for the 90 dB SPL series. At the side contralateral to the applied stretch first an increase in SP is found which returns to its original value after COCB transection (Fig 37). A similar pattern of changes is noted for the amplitude of the cochlear microphonics (Fig 38). The effects are summarized in Table X.

Table X: The effect of stretch of the vestibular nerve followed by transection of the COCB on the ipsilateral ear

	effect of stretch	subsequent COCB transection
N_1-amplitude	decreased*	no change
N_1-latency	increased*	no change
AP-waveform	monophasic*	returns to diphasic*
SP-amplitude	decreased	no change
CM-amplitude	decreased*	no change

9.3 Transection of the followed by stretching the vestibular nerve

In four animals the experimental manipulations have been reversed. No recordings from the contralateral ear have been made.
The N_1-amplitude measured at 40, 60 and 80 dB SPL appears to be slightly increased after section of the COCB, subsequent stretch of the vestibular nerve results in a small amplitude reduction (Fig 39) as shown in Table XI.

Table XI: The effect of COCB transection and subsequent vestibular nerve stretching on the AP amplitudes

A_{N_1}-ratio	A	B	C	D
transection COCB 40 dB SPL	1.09	1.30	0.82	1.05
stretch vest. nerve	0.75	0.60	1.00	0.13
transection COCB 60 dB SPL	1.15	1.10	1.30	2.01
stretch vest. nerve	0.87	0.91	0.80	0.97
transection COCB 80 dB SPL	1.04	1.00	1.07	1.10
stretch vest. nerve	0.99	0.92	1.00	0.49

The first row in each intensity section refers to the effect of transection, the second intensity row to the combined effect of transection and vestibular nerve stretching.
The N_1-latency is reduced after COCB section and increases again after stretching the vestibular nerve.
The waveform of the compound AP is not affected by stretch of the vestibular nerve when the COCB is first transected.
The effect upon the SP and CM amplitude are variable (Fig 40 and Fig 41) in that stretch always produces a reduction in SP but the previous transection had variable effect, while the CM changes are irregular to both influences. Table XII summarizes the findings.

Table XII: The effect of transection of the COCB followed by stretch of the vestibular nerve

	effect of transection	subsequent stretch
N_1-amplitude	increased*	decreased*
N_1-latency	decreased*	increased*
AP-waveform	no change	no change
SP-amplitude	variable	decreased*
CM-amplitude	variable	variable

9.4 Discussion

The effects of vestibular nerve stretch upon the parameters of the AP could be explained by the assumption of increased efferent activity (cf section VIII.7). The results with respect to the CM and SP, however, merely pointed to a reduced efferent activity after vestibular nerve stretch.
In the first set of experiments (Table X) it is demonstrated that after stretch of the vestibular nerve only the waveform of the AP is restored by transection of the COCB. Of the cochlear potentials the SP also shows a tendency to restore after COCB-transection. In the second set of experiments, where the manipulations on the nerves are reversed not a single parameter is influenced when the COCB is transected prior to stretch of the vestibular nerve. The N_1-amplitude and the N_1-latency were however slightly influenced by COCB transection and this was partially restored by stretch of the vestibular nerve (Table XII). Combining both sets of experiments it becomes likely that stretch of the vestibular nerve interferes at least with activity in the COCB. The experimental results in bilateral recording and vestibular nerve stretch followed by COCB transection reflect the influence of the crossed efferent fibers on contralateral activity. The effects of vestibular nerve stretch after COCB transection on the N_1-amplitude and the N_1-latency probably indicates an effect on the uncrossed efferent nerve fibers. This uncrossed efferent system is much more important than previously thought (Warr, 1975).
From the experimental results presented here a working model for the mechanism of stretch of the vestibular nerve is based on

1). An effect of the COCB is mainly and exclusively on the AP-waveform and N_1-amplitude.
2). Interacting effects of the COCB and UOCB especially on the homolateral N_1-amplitude, N_1-latency, CM and SP.
3). Effect of the COCB exclusively on the contralateral N_1-amplitude, N_1-latency, and SP.

9.5 Systemic drug application interfering with selective stretch of the vestibular nerve

In four animals selectively stretching the vestibular nerve was followed by intravenous administration of strychnine-nitrate (0.2 mg/kg), which acts as a selective blocking agent of efferent nerve activity (Desmedt, 1962; Daigneault, 1966; Rubenstein et al., 1976).
The effect is illustrated in Fig. 42 with respect to the input-output curve in an individual animal.
The amplitude reduction caused by stretch of the vestibular nerve is nearly completely restored *immediately after* i.v. application of strychnine-nitrate. The effect on the AP-waveform (Fig 43) is the same as that of COCB transection. The more or less monophasic narrowband responses e.g. at 5.3 kHz are restored to normal. The effects upon CM and SP (Fig. 44) also illustrate the partially compensating action of strychnine. Summarizing: *all* the effects of vestibular nerve stretch are to a large extent, but not completely, restored to their initial values. This might form an estimate of which part of the effect is due to an unspecific, e.g. metabolic, action.

9.6 Local application of KC1

In six animals the effect of local KCl-application (1 mgr KCl in 10 ml H_2O solution on the vestibular nerve is studied. A tiny piece of gelfoam® (1 × 1 mm) was soaked in KC1 solution and placed on the vestibular nerve. Nevertheless diffusion of KCl might also cause an interference with the auditory nerve. The unspecific hyperpolarization produced by KCl blocks the afferent as well as efferent activity in the auditory and vestibular nerve. In all experiments it was observed that it took some time (2 to 3 minutes) before the effect was maximal, this clearly contrasts the effect of stretch applied on the nerve. Therefore the effects are supposed to be caused by KCl and not by pressure during the application itself. The effects are considered with respect to the usal parameters.

9.6.1 The N_1-amplitude

The increase in the N_1-amplitude generally occurs 2-3 minutes after application. The higher intensity AP's are always affected earlier than the lower intensities, and also show a tendency to return quicker to their original value after cessation of the KC1-action. In general KC1 produces a slight increase (Fig. 45) in the I/O curve, 2 hours after the application after irrigating with physiological salt solution (Ringer) the curve is generally restored to its initial values. On the contralateral ear (Fig. 46) there appears to be an effect too which also restores after two hours.

9.6.2 The N_1-latency

The latency of the N_1 is increased after KCl-application (Fig. 47). Two hours later the normal values are obtained again.

9.6.3 The AP-waveform

The effect on the AP-waveform is illustrated for a low (30 dB) and a high intensity comparing the initial waveform and the recordings after 2, 15 and 90 minutes. The effect is quite clear and qualitatively the same as produced by stretch of the vestibular nerve. (Fig. 48). At the contralateral ear no change in the waveform was recorded, this rules out diffusion of KCl to the contralateral side.

9.6.4 The cochlear potentials

The SP as well as the CM amplitude are reduced after local application of KCl (Fig. 49). On the contralateral side SP and CM also appeared to be reduced in contrast again to the AP-amplitude (Fig 50, Fig 51).
The effects are summarized in Table XIII.

Table XIII: Homo and Contralateral effects of KCl-application

	Homolateral	Contralateral
N_1-amplitude	increased*	increased*
N_1-latency	increased*	increased*
AP-waveform	monophasic*	no change
SP-amplitude	decreased*	decreased*
CM-amplitude	decreased*	decreased*

9.7 Discussion

The results of local KCl application can be explained on basis of afferent nerve block as well as efferent nerve block at least on the side of application.
On the contralateral ear one conceives that the COCB would be effected and that the changes are mediated by the efferent system. The increased N_1-amplitude and reduced receptor potentials can be explained on basis of a reduction in the activity of the COCB, since the effects partially contrast those of electrical activation of the COCB (cf VIII.7).
At the application site afferent nerve block could produce an increase in AP-amplitude and AP-latency as well as the change in waveform. Since the effects on the AP are the opposite of vestibular nerve stretch with respect to the N_1-amplitude only a combined action of KCl on afferent and efferent nerves will be most likely (see also Legouix et al., 1978).
In order to know whether afferent activity is blocked by KCl application on the vestibular nerve recordings of brainstem potentials are crucial. These will be described in the next chapter.

X Recording of Brainstem-potentials

A bipolar electrode is placed on the cerebral hemisphere on a location permitting the distinction of the individual peaks in the brainstem evoked potentials. Attention is focussed on the peak-to-peak latency differences and the waveform since these parameters are the more vulnerable and of importance in detecting acoustic neurinomas in man (e.g. Selters and Brackmann, 1977).

10.1 Selective stretch of the vestibular nerve, followed by strychnine administration

Selective stretch of the vestibular nerve generally results for the AP in an amplitude decrease, latency increase and a change toward a monophasic waveform. Intravenous administration of strychnine nitrate greatly restores these changes (cf XI.5). In addition these effects have been studied for the brainstem responses (Fig. 52).
One of the primary effects of selectivity stretching the vestibular nerve, besides the decrease in wave I (similar to the N_1 in the round window recording) amplitude decrease and a latency increase, is that the clear separation into distinct waves I, II, III and IV almost completely disappears. Strychine administration restores the brainstem potentials to a major extent.

The effects of vestibular nerve stretch have been repeated for 3 other animals and the effects upon latency for the various waves are shown in Table XIV.

Table XIV: Latency changes for the brainstem potentials induced by stretch of the vestibular nerve

100 dB	wave I	II-I delay	III-II delay	IV-III delay	V-IV delay
$\Delta\tau$	+ 0.3	+ 0.1	+ 0.05	+ 0.10	+ 0.30
	+ 0.1	+ 0.35	− 0.05	+ 0.05	+ 0.25
	+ 0.05	+ 0.35	+ 0.20	+ 0.50	+ 0.70
	0.0	− 0.25	− 0.10	− 0.05	+ 0.15

In general one concludes that stretching the vestibular nerve produces a latency increase for wave I, while the delays between waves I, II and III do not change significantly. Fot the later waves the delays start to increase again. This points more into the direction of changes in the brainstem at the level of generation of waves VI/V or difficulties with the identification of the later waves, than so consistent latency changes at more peripheral location as mostly found in human brainstem recordings.

10.2 Application of KCl

Repeating the experiments from section IX.6 one observes for the brainstem responses a loss of synchrony for the individual waves thereby producing a broad irrigular brainstem response super-imposed upon a dc shift. It appears (Fig. 53) as if the afferent activity in the auditory nerve is not blocked completely, but synchronous firing of the individual fibres is lost.

10.3 Discussion

In general, lesions in the animal's brainstem or pontine angle reduce the amplitude of a particular wave and especially the later waves. So far no reports deal with the latency changes in animals (Starr, 1977). The major finding in brainstem responses recorded from the human skull in cases of acoustic neuromas or lesions in the brainstem is an increase in the delay between the various waves and in more serious stage the loss of the complete response pattern (e.g. Selters and Brackmann, 1977). The findings shown here fail to produce latency changes up to wave III (the contralateral olivary complex region) while the later waves (supposed to originate from the contralateral side of the brainstem) do show increases in latency. Due to the general fuzzy appearance of the BSER in these cases where 'minimal' stretch was applied these findings must be interpreted with reserve. The most consistent finding is the blurring of the BSER, a fact well known as an indication for some malfunctioning but not indicating precisely what is happening.
The results for KCl suggest an incomplete nerve block, presumably only the more basel (superficial) fibers are blocked. This would result first of all in a more pronounced decrease of wave I than for wave IV while the response also broadens (Don and Eggermont, 1978). Effectively a desynchronization of the firings in the central part of the eighth nerve will certainly result in change of the narrow-band action potentials from dispasic to a more monophasic appearance, thereby explaining the gross changes in the AP-waveform after KCl-application.

XI General Discussion

11.1 Introduction

Mechanical interference with the VIIIth cranial nerve influences the neural response (AP) as well as the receptor potentials (CM and SP). Selective mechanical interference with the cochlear and vestibular nerve has different and opposite results (VIII.3, VIII.5). The type of mechanical interference (stretch, transection) of each VIIIth nerve division has different results (VIII.2,3; VIII.4,5). In experiments on the vestibular nerve changes have been demonstrated in the responses recorded from the contralateral ear (VIII.6). These various observations suggest, that a rather specific mechanism is involved in mechanical interference with the vestibular nerve. It is very likely, that this mechanical interference alters the activity of the efferent nerve system, since the efferent nerve fibers to the cochlea run along the vestibular nerve (III.2).
The experimental data in the literature and the results presented in the underlying study about the role of efferent innervation of the cochlea are, however, not in entire agreement. It will be shown, that the model of efferent innervation as designed by Wiederhold can not adequately explain the experimental findings in the present study. Also the changes in the AP-waveform are not fully understood by the classic Keith-Lucas model (Davis, 1976). Finally an effort will be made to design a new model, which does agree with the known experimental data and also explains the result in the present study. In the present study a decrease of the N_1-amplitude was found after homolateral stretch of the vestibular nerve and after partial transection of the cochlear nerve. An increase of the N_1-amplitude was recorded after transection of the vestibular nerve, transection of the crossed olivo cochlear bundle, and after application of KCl on the eighth nerve.
Stimulation of the crossed olivo cochlear bundle with electical shocks results in a reduction of the AP-amplitude (Sohmer, 1966). The cochlear microphonics were found to increase after COCB electrical stimulation (Konishi and Sleptan, 1970), the AVE SP^- appeared to be reduced, while the AVE $SP\propto$ increased (Gans, 1977). For round window recordings this would correspond to an amplitude increase of CM and SP, for high frequency stimuli.

Under the assumption, that stretching the vestibular nerve results in an increased efferent activity the changes in the AP can be explained, and also the restoring capabilities of intravenously applied strychnine (an efferent blocking agent) after vestibular nerve stretch (IX.5) become understandable.
Transection of the vestibular nerve is assumed to decrease the efferent inhibitory influence, thereby explaining the increase of the AP-amplitude. Stretch and transection of the vestibular nerve deal with the crossed and uncrossed efferent nerves. Transection of the crossed fibers only, results in a slight increase of the AP-amplitude (IX.3).
Subsequent stretch of the vestibular nerve in this condition will then result in an increase of uncrossed efferent nerve activity only. The reduction of the AP-amplitude due to stretching the vestibular nerve, after COCB transection, was found to be only minor (IX.3 and Fig. 39). This suggests, that the crossed efferent fibers produce the major part of the inhibitory influence on the AP-amplitude. This has been confirmed by separate electrical stimulation of the uncrossed and crossed olivocochlear bundle (Sohmer, 1966).
So far the effects of selective experiments on the vestibular nerve are well explained by a changed efferent nerve activity according to the shunting model (Wiederhold, 1962).
However, for a complete validation of this hypothesis on efferent nerve activity one also has to consider to influence on the cochlear potentials. In experiments on the vestibular nerve, in which the efferent nerve activity was supposed to be increased, however a reduction of the CM and SP amplitudes was found (VII 2,4).
According to the presented shunting model an increased activity in the efferent nerve fivers should result in an increase of cochlear potentials (Gans, 1977). In experiments on electrical stimulation of the COCB this has also been found (Konishi and Slepian, 1970).
It is therefore concluded, that this model does not explain our experimental results on the cochlear potentials, therefore an alternative model partially updating the previous one, is proposed.

11.2 The Shunting Model

This so called shunting model of efferent innervation, has been proposed by Wiederhold (1962) and recently adjusted by Geisler (1974). In principle this model is based upon the specific influence of the efferent nerve action on the permeability of the outer hair cell membrane. Direct influence of the efferent nerve activity on the permeability of the outer hair cells for small ions has been indeed been demonstrated (Flock and Russel, 1973; Desmedt and Robertson, 1975). Increased efferent nerve activity leads to a larger dc current through the outer hair cells, thereby producing larger CM and SP. Since the total current is assumed to be constant a smaller dc current goes through the inner hair cells, leading to a reduced AP. A schematical representation of this so called shunting model is shown in Fig 54. It is taken into account, that the major contribution to the cochlear potentials comes from the outer hair cells, while 90-95% of the afferent nerve fibers innervate the inner hair cells, which will therefore generate the major part of the AP.

11.3 Towards a new model

11.3.1 Outline

In order to explain the experimental results in the present study by a new model several facts have to be taken into account.
In the experiments in which stretch was applied on the vestibular nerve, it was presumed that this mechanical interference would result in an increased efferent nerve activity. In clinical and experimental studies it has been shown, that neural transmission can, however, be blocked by gentle touch or local pressure on the nerve (Seddon, 1943; Londen, 1976). This phenomenon is known as neurapraxia (non acting nerve).
In studies on the efferent innervation of the cochlea it has been shown that not only myelinated nerve fibers contribute to the cochlear efferent innervation, but also unmyelinated efferent fibers (Terrayama et al., 1969). Mechanical interference with the vestibular nerve as carried out in the present study might well have a different influence on either myelinated and unmeylinated efferent fibers. This should be incorporated in the outline of a new model.
Finally, experiments have shown that a separate system of innervation of outer and inner hair cells by crossed and uncrossed efferent fibers does exist (Warr, 1977). The unmyelinated and myelinated efferent nerve fiber distribution, its possible different behaviour on mechanical influence and the distribution along inner and outer hair cells should be taken into account in the design of a new model.

11.3.2 The neurapraxia phenomenon

In clinical and experimental studies it has been shown, that neural transmission can be blocked completely by gentle touch or local pressure upon the nerve (Seddon, 1943; Landon 1976). This phenomenon is known as 'neurapraxia' and may be defined in a peripheral (motor) nerve as an injury in which paralysis occurs in the absence of peripheral degeneration. There is a complete conduction block but the anatomical continuity of the axon is preserved. After a quiescent period, which may persist for as long as 3 months, but usually is of shorter duration, the nerve conduction across the affected segment returns to normal. The phenomenon of neuropraxia is supposed to be mediated by a mechanical interference with the myelin nerve sheet and is therefore probably restricted to myelinated nerve fibers. Unmyelinated nerve fibers seem somehow resistant to milder forms of acute local compression (Fowler and Ochoa, 1975), which does not seem to conflict with their greater sensitivity to mechanical stimuli (Lindquist, 1973). When local pressure is excerted on a non peripheral, cranial nerve, the neurapraxia phenomena may also occur. This has been frequently observed in studies on the facial nerve (Campbell et al., 1962, Sunderland, 1977). A case of apraxia of the VIIIth cranial nerve due to local pressure of an arachnoïd cyst on the acoustic nerve has also been described (Innitzer, 1976 b).
The various studies in vitro on responses of nerve fibers subjected to mechanical forces have been reviewed by Goldman (1971). Mechanical forces, which impinge on the axon are fundamentally compressive or shearing.
Stretch as used in this study results actually in a composite strain. No systemic studies have been made on the various kinds of mechanical stimulation, probably because of the great difficulty to carry out clean experiments. In in vitro experiments it has been found that unmyelinated nerve fibers can be stretched up to four times their initial length with relatively little change in conduction (Jenkins and Carlson, 1904; Goldman, 1964). Another experiment has shown that short rapid mechanical stimuli can produce action potentials and that subthreshold mechanical stimuli can produe a very long lasting depolarisation (Julian and Goldman, 1964).
In this way the effects of local stretch or compression mimic the responses of certain mechanoreceptors as for example the pacinian corpuscles (Loewenstein, 1965; Gray, 1959), and it has been suggested that the axon may be an elementary model for mechanoreception. This model holds for in vitro experiments. For in vivo experiments of the muscle spindle it has been demonstrated that at the synapse of the so called flower-spray endings stretch does initiate a response.

11.3.3 The projection of the efferent nerve system

The efferent innervation of the cochlea consists of myelinated and unmyelinated nerve fibers in a ratio of 3 : 2 (Terrayama et al., 1969). The exact course of these fibers to inner and outer hair cells is not known, however. It seems quite likely, that when local pressure, or stretch is applied to the vestibular nerve, myelinated and unmyelinated efferent nerve fibers will be affected in different ways. According to what is known about mechanical interference on these nerves, the nerve conduction in myelinated efferent fibers is assumed to be blocked by neurapraxia, and the nerve activity in unmyelinated efferent fibers will be increased according to the mechanoreceptor model.
To account for the reduction of the CM and SP, as well as for the AP reduction after vestibular nerve stretch, another assumption is required in this experimental model: the myelinated efferent nerve fibers must terminate upon the outer hair cells and the unmyelinated upon the afferent dendrited to the inner hair cells. No direct experimental evidence has so far been avaiable to back this assumption. Recent experiments have shown a separate system of innervation of outer and inner hair cells by crossed and uncrossed efferent fibers (Warr, 1978). The outer hair cells are mainly innervated by crossed fibers (69%), the inner hair cells, however, by as much as 86% of the uncrossed nerve endings. This indicates that interference with the uncrossed efferent fibers would especially affect the AP-amplitude and has only a minor effect upon the cochlear potentials.

11.3.4 Concepts for a new model

So far the following assumption have been made for the extended model:

1. a. Stretch results in a conduction block (neurapraxia) of myelinated fibers (Sunderland 1977, Innitzer, 1976).
   b. Stretch results in an increased activity in unmyelinated nerve fibers (Goldman, 1971; mechanoreceptor model).
2. a. Crossed efferent nerve fibers terminate on the outer hair cells (Warr, 1975; Nakai et al., 1974).

b. Uncrossed efferent nerve fibers terminate on the afferent dendrites innervating the inner hair cells (Warr, 1975).

3. a. Myelinated efferent nerve fibers mainly innervate the outer hair cells.
   b. Unmyelinated efferent nerve fibers mainly end on the afferent dendrites to the inner hair cells (Warr, 1978).

A schematical representation of the effects produced by selective stretch of the vestibular nerve based on these assumptions is shown in Fig 55.

11.4 Comparing the model with the experimental results

The proposed model can now be evaluated according to the experimental results (VIII, IX, X). In table XV the various model results have been evaluated. The theoretical results are obtained by considering the proposed efferent nerve activity upon the outer and inner hair cells. The resulting parameters can be calculated by adding up the individual contribution. A direct influence through field potentials from outer on inner hair cells has not been taken into account.

Table XV 1. In experiments on selective stretch of the vestibular nerve it is assumed that the reducing influence on the AP, due to increased efferent activity of the uncrossed unmyelinated fibers on the inner hair cells exceeds the increasing effect of efferent nerve blockade of crossed myelinated fibers to the outer hair cells. Transection experiments of the crossed olivocochlear bundle have shown that the increasing effect on the N_1-amplitude is only moderate (IX.3).
The theoretical result on selective stretch of the vestibular nerve does agree with the experimental results presented on VIII.3.
In experiments on the vestibular nerve it has been found that the effects of stretch last for at least 60 minutes. The AP-reduction is explained by increased efferent activity of the unmyelinated uncrossed efferent fibers. Although the effect of neuropraxia on the myelinated fibers may last for a considerable time it seems quite unlikely that the increased efferent activity could be of such a long duration. Unless some tonic hyperpolarisation is assumed to occur at synapse level the duration of the resultant effect after vestibular nerve stretch is inadequetely explained by this model.

Table XV 2. When the vestibular nerve is transected the cochlea will be disrupted from crossed and uncrossed efferent innervation. The result of this experiment should actually be similar to the application of KCl on the vestibular nerve (X.2). When strychnine indeed blocks efferent nerve activity, the results of those studies should also be considered here (Rubenstein et al., 1976). The model predicts a reduction of the cochlear potentials and an increase of the AP-amplitude. The experiments showed a slight increase of the N_1-amplitude while the cochlear parameters were not affected (VIII.4). The experimental results of KCl application fully agree with the predicted theoretical outcome, while in experiments with strychnine administration the N_1-amplitude was found to be increased (Rubenstein et al., 1976).

Tabel XV

model	effect upon eff. system	amplitude CM	SP	AP
1. Vest. N. Stretch				
O.H.C.	block	↓	↓	↑
I.H.C.	↑	=	=	↓↓
Model result		CM↓	SP↓	AP↓
2. Vest. N. Transection				
O.H.C.	block	↓	↓	↑
I.H.C.	block	=	=	↑↑
Model result		CM↓	SP↓	AP↑
3. Electr. Stim. UOCB				
O.H.C.	=	=	=	=
I.H.C.	↑	=	=	↓
Model result		CM↑	SP↑	AP↓
4. Electr. Stim. COCB				
O.H.C.	↑	↑	↑	↓
I.H.C.	=	=	=	=
Model result		CM =	SP =	AP↓
5. COCB transection Vest. N. Stretch				
O.H.C.	block =	↓ =	↓ =	↑ =
I.H.C.	= ↑	= =	= =	= ↓↓
Model result		CM↓	SP↓	AP↓
6. Vest. N. Stretch COCB transection				
O.H.I.	block block	↓ ↓	↓ ↓	↑ ↑
I.H.C.	↑ =	= =	= =	↓↓ =
Model result		CM↓	SP↓	AP↓
7. Vest. N. Stretch Strychnine adm.				
O.H.C.	block block	↓ ↓	↓ ↓	↑ ↑
I.H.C.		= =	= =	↓↓ ↑↑
Model result		CM↓	SP↓	AP↑

Table XV 3. The results of selective electrical stimulation of crossed and uncrossed efferent nerve fibers have also been calculated according to this theoretical model. Electrical stimulation of the uncrossed olivo cochlear bundle theoretically results in an AP-amplitude reduction only. This has been confirmed by Sohmer, 1966, who demonstrated AP-reduction and no effect on the CM after homolateral electrical stimulation.

Table XV 4. The experimental results of electrical stimulation of the crossed olivo cochlear bundle have been reviewed in IV.3. The theoretical results therefore agree with the experimental findings.

Table XV 5. The theoretical model can be further analysed on the combined experiments of transection of the crossed olivo cochlear bundle followed by stretch and in reverse order as presented in IX. The calculated theoretical result of transection of the crossed olivo cochlear bundle would be a reduction of cochlear potentials and N_1-amplitude increase. Subsequent stretch of the vestibular nerve should only result in increased uncrossed efferent activity which reduces the AP-amplitde. The combined result should be a reduction of all parameters in these experiments. These theoretical results have been confirmed (IX).

Table XV 6. For the reversed experiment in which first stretch is applied to the vestibular nerve and then the olivo cochlear bundle is transected the theoretical results are similar with the experimental findings presented in Table X, Chapter IX.2. The SP-amplitude shows no change towards after COCB transection. In order to interpret this difference it is of interest to know more about the blocking mechanism produced by the neuropraxia mechanism and of olivo cochlear bundle transection. Also the blocking mechanism of strychnine should be discussed in some more detail.

Table XV 7. In this experimental part selective stretch of the vestibular nerve was for example followed by administration of strychnine. The model result for this experiment does, however, not agree with the experimental findings. In case of strychnine administration after vestibular nerve stretch not only the AP-amplitude almost completely returned to normal, but also the cochlear potentials.

Summarizing: the various experimental results are generally well explained by this theoretical model. The model does not account for the results of strychnine administration after vestibular nerve stretch.
It has been assumed that selective stretch of the vestibular nerve results in a conduction block of the myelinated crossed efferent fibers, while the efferent nerve activity in unmyelinated efferent fibers is supposed to be increased. By the administration of strychnine, which acts as a blocking agent of efferent nerves, the effect on the myelinated crossed nerves should be supportive, while the inhibiting effect on the inner hair cells should be blocked, resulting in an increase of the reduced AP-amplitude. This last observation has indeed been made. The cochlear potentials were, however, also restored after strychnine adminsitration. Although the mechanism of neurapraxia is unknown it is quite possible that the blocking effect is mediated on the

membrane permeability resulting in a blockade of K^+-ion repolarisation.
Although the blocking mechanism of strychnine is not definitely settled, experimental results have shown that its action could well be presynaptic, inhibiting acetylcholine release (McKinsley and Koelle, 1967; Guth and Bobbin, 1971). The result of the individual blocking actions: neurapraxia by tonic depolarisation due to blocked K^+ repolarisation, and strychnine by inhibiting acetylcholine release, could therefore well compensate each other. This would explain the restorting influence of strychnine on the CM and SP-amplitudes.

The interpretation of the various experimental data related to the efferent nervous system activity presents several problems itself. The reducing effect of electrical stimulation of the uncrossed efferent fibers on the N_1-amplitude is less than the inhibiting effect of electrical stimulation of the crossed fibers on the N_1-amplitude (Sohmer, 1966). This observation has been supported by the experimental results presented in Chapter IX, which showed that after transection of the COCB, the N_1-amplitude reduction caused by stretch of the vestibular nerve and mediated through the uncrossed efferent fibers was only minor. Recent results on the anatomy of the efferent nervous system have shown that the inner hair cell are mainly supported by uncrossed efferent fibers (Warr, 1975). Although the innervation of inner hair cells is mainly by uncrossed efferent fibers, the experimental results on electrical stimulation, transection of the COCB followed by stretch, have shown that, the indirect inhibition through the crossed efferent fibers on the outer hair cells is more effective.

11.5 Model explanation for the AP-waveform

The waveform of the AP has received special attention in the study of retrocochlear disorders in man (Aran et al., 1973; Eggermont, 1976; Beagly et al., 1977) but Brackmann and Selters (1976) already showed that an abnormally broad waveform was not a necessary condition for the presence of an acoustic neuroma. The compound AP waveform is the result of various interacting phenomena: the waveform of the unit contribution, the degree of cochlear filtering determining the synchronization between the units, and the specific electroanatomy of the preparation (Teas et al., 1962; de Boer, 1975; Eggermont, 1976 b).

One goal of this study has been to find out if various AP-waveforms and stimulus response relations as actually found in electrocochleography in acoustic neurinoma cases, can be related to a different location and action of these tumors. From this study the change into a broad monophasic waveform appeared to be one of the more consistent results of nearly every type of interference, even if restricted to the vestibular nerve.
Since the intermingled SP was invariably of positibe sign the broad waveform could not be explained on interference of AP and SP. Narrow band derivation (VIII.4.5) showed that the phenomenon is also seen in more restricted parts making it plausible that the phenomenon is due to changes in the unit waveform (cf Eggermont, 1976 a).

11.5.1 Ionic mechanisms

The generation of a unit impulse, or action potential, is governed by the conductance of (K^+) and (Na^+) and (Cl^-) through the nerve fiber membrane, and can be mathematically expressed by the Hodgkin – Huxley exquations (Hodgkin and Huxley, 1953). The changes in ion conductances during stimulation will influence the electrical changes in the nerve fiber membrane. Excitation depends on the activation of the (Na^+) conductance, depolarisation will continue until the recovery process (sodium inactivation and voltage dependent K^+ conductance increase) starts. The moment at which the repolarisation process is initiated will influence the action potential configuration. In the absence of any recovery process the membrane potential would become stable at its depolarisation level (Noble, 1966). Thus any factor influencing the ion conductances may affect the depolarisation and repolarisation process and therefore the recorded action potential waveform.

11.5.2 Effects of the effent system

Electrical stimulation of the COCB appears to increase the ion conductance in the membranes of the auditory nerve dendrites and the outer hair cells (Desmedt and Robertson, 1975). According to these authors several indirect arguments are in favour of the postsynaptic efferent axo-dendritic mechanism. Selectively stretching the vestibular nerve was assumed to increase the activity in the uncrossed unmyelinated efferents and to block the activity in the crossed myelinated fibers. This increase in efferent activity will increase the (Cl^-) conductance in the axo-dendrite junction of the inner hair cells. This change in ion conductance will influence the electrical proporties of the nerve fiber membrane and may effect the depolarisation and repolarisation process and therefore the recorded action potential waveform. According to this model the monophasic broad AP-waveform observed after selective stretch of the vestibular nerve might well be a steady state condition due a change in ion conductance.
In this study it has been demonstrated that the monophasic AP-response after vestibular nerve stretch can be restored by strychnine administration (X.1.). Strychnine probably inhibits the acetylcholine release and therefore blocks the depolarisation steady state, and repolarisation can occur (XI.4). Although the concept of changed ion conductance seems rather useful, not all experimental results can be that easily explained. The monophasic AP-wave after stretch of the vestibular nerve was immediately restored to normal by COCB transection (IX.2). Since it was assumed that the crossed efferent mainly innervate the outer hair cells, transection of the crossed fibers should not affect the AP-waveform unless a presynaptic inhibitory mechanism should occur. The same holds when the COCB was first transected, followed by vestibular nerve stretch and no marked change was found to occur in the AP-waveform. A broadened AP-waveform resulted also from partial transection and stretch of the cochlear nerve.

11.5.3 The Keith-Lucas Model

Classically a biphasic AP is explained by the Keith-Lucas model (Davis, 1976). The assumption, however, that in most recording situations both electrodes have the same characteristics with respect to the nerve on both sides of the meatus can be questionned. There is no doubt that the round window electrode and the reference electrode in the neck muscles have quite different proportions. This can easily be demonstrated by grounding the reference electrode, which causes only a hardly perceptible difference in waveform. It seems therefore, that as a working hypothesis the two-electrode system is not adequately founded. An alternative approach to this situation is with one sensing electrode on the nerve origin (i.e. Round window-perilympt) and a reference electrode in a remote position. Classically one expects a positive-negative-positive type of AP that (while recording from the nerve end) reduces to a negative-positive diphasic AP. In case of a conduction block (e.g. by a transection in the internal meatus) this confirguration also results in a monophasic AP, which generally will have a slightly increased amplitude and latency (cf Fig 56) compared to the diphasic one.
After partial transection of the cochlear nerve, however, the AP amplitude was reduced in such a way that the AP to higher frequency (6 kHz) tonebursts was more affected that to the lower frequencies (2 kHz). Thus it is likely that transection reduced the number of exitable fibers.
In contrast stretching the cochlear nerve produced a monophasic response with increased AP-amplitude. When stretch of the cochlear nerve is also considered as a block (neuropraxia) this enhanced AP-amplitude would fit the model prediction (e.g. Teas et al., 1962; Legouix et al., 1978).

11.6 Clinical implication

The aim of this study has been to find out if the AP-waveform and stimulus-response relations, actually found in electrocochleography in acoustic neurinomas, can be related to the different location and action of these tumours. In various clinical studies on electrocochleography in acoustic neurinomas special attention has been paid to the AP-waveform and other stimulus response relations (Morrison et al., 1976; Gibson et al., 1977; Brackmann, Selters, 1976; Legouix et al., 1978; Innitzer, 1976; Eggermont, 1976 a; Aran, 1973).
In producing experimental retrocochlear lesions the present study has shown that the characteristically broad AP-waveform appears regardless the location of the mechanical interference with the eighth nerve. Selective mechanical interference with the vestibular nerve which runs a separate course from the cochlear nerve in guinea pig, produces a characteristic change in the recorded AP-waveform.
According to the shape of the recorded AP response no distinction could be made whether the experimental lesions regarded the vestibular or the cochlear nerve. Application of KCl, producing a conduction block of the eighth nerve also showed a typical monophasic AP-waveform. Although in this experimental study the monophasic AP-waveform was found to be characteristic for any interference in the pontine angle, it has been shown in clinical studies that the AP-waveform can be absolutely

normal in the presence of retrocochlear lesions (Brackman and Selters, 1976).
It is therefore concluded that if in clinical electrocochleography abnormalities in the AP-waveform are found strong evidence is thereby provided for the presence of a lesion in the pontine angle. The site and type of lesion, however, cannot be inferred from this finding. Besides that most acoustic neurinomas produce cochlear lesions by the gradual depression of cochlear blood flow (Eggermont et al., 1979) it has repeatedly been shown (e.g. Aran and Negrevergne, 1973) that high frequency hearing loss also causes abnormally broad AP waveforms. The use of brainstem electric responses in the detection of acoustic neuroma (Selters and Brackmann, 1977, Clemis and McGee, 1979) is mainly based on the increase of the latency difference between waves V for both ears, and seems to offer very good results. It is surprising that in experimentally induced lesions (this thesis, Starr & Achor, 1978) the most consistent finding is a decrease in amplitude and not a specific latency increase. It seems that the problem of the action of acoustic neuroma on the auditory system in man is far from being resolved. The material presented in this study, however, offers some mechanisms which may be responsible for part of the findings obtained in patients.

11.7 Limitations

For the explanation of all of the observed findings we could not rely entirely upon proven evidence from histology and nerve fiber physiology. Some unexplained experimental results could be due to inadequate lesions which were not verified by histological techniques. The mechanical interference on the vestibular nerve (although a very gentle procedure by itself), might still affect the cochlear blood supply and metabolism. Compared with the slowly developing extension of a tumorprocess in the cerebellopontine angle, this mechanical interference remains a brisk manoeuvre.
In the outline of a new model several ad hoc assumptions had also to be incorporated. In addition we have to be aware of the case at which a mainly unknown system, as the auditory efferent nerve system, can be used to explain certain findings. Since the discovery of the efferent auditory system various properties have been attributed to its action. Most of these properties have been ruled out by subsequent experiments. Nevertheless this thesis on mechanical interference with the vestibular nerve has made a marked influence of efferent nerve activity on the electrical response of the eighth nerve, however, very likely.
The exact role and action of the efferent system in case of mechanical interference with the vestibular nerve, waits for further anatomical evidence about the number and distribution of uncrossed and crossed efferent fibers, as well as the distribution of myelinated and unmyelinated efferent fibers in the cochlea. Very recently the distribution of the efferent fibers to the inner and outer hair cells has been studied (Warr, 1978).
It has veen shown that the crossed fibers mainly (68%) terminate on the outer hair cells and the uncrossed fibers in majority (86%) on the inner hair cells. It appears that the rather different outcome of the study by Warr (based on axonal uptake of horseradish peroxidase) with respect to the older studies (based on myelin staining techniques) is a very strong indication that the uncrossed fibers found in large numbers are unmyelinated nerve fibers. These observations confirm the hypothesis made in XI.3d.

Chapter I

A general description is given of cerebello-pontine angle tumours with special reference to acoustic localisation of this tumour and its macroscopic and microscopic appearance are reviewed. The clinical symptoms and the various diagnostic tests in the clinical diagnosis of these tumours are discussed and their liability is evaluated. In outlining the surgical treatment of these, principal benign lesions, emphasis should be on early recognition in order to achieve complete surgical removal with eighth and seventh nerve function preservation.

Chapter II

The effects of an acoustic neurinoma can be reproduced in an animal experiment by compression of the surrounding structures in the cerebello-pontine angle. The use of an inflatable balloon has been disregarded in guinea pig experiments because concomittant pressure effects are inevitable due to balloon explacement. In this animal model the effects of acoustic neurinomas were mimicked by selective stretch and transection experiments of the vestibular and cochlear nerve.

Chapter III

The gross anatomy of the cerebello-pontine angle in guinea pig is briefly presented. Special attention is given to the anatomy of the efferent nervous sytem. Efferent nerve fibers to the cochlea pass along the vestibular nerve and consist of crossed and uncrossed olico-cochlear bundles. The main distribution of crossed fibers is to the outer hair cells with synaptic contact at the base of the outer hair cell. The uncrossed efferent nerve fibers probably have direct axo-dendritic synaptic contact with the inner hair cells.

Chapter IV

The role of the efferent nervous sytem is still unknown. Various studies have been designed to study the role of efferent nerve innervation. Electrical stimulation studies have demonstrated an inhibitory influence on the afferent audiotory input. Transection studies of crossed and uncrossed efferent nerve fibers have also shown its inhibitory influence on the afferent input, and, also an effect on the recorded waveform. In behavioral auditory research no direct influence of efferent innervation could be demonstrated in transection experiments. The inhibitory-influence is probably mediated by a ACh. transmitter by postsynaptic inhibition.
Although various effects have been attributed to the influence of efferent nervous system its functional significance is still not known.

Chapter V

In this chapter the design and motivation of the experiments in this study are outlined. Clinical studies have shown that electrocochleography and the recording of brainstem responses may show some characteristic findings in retrocochlear pathology. In this study various experiments are designed in order to see whether retrocochlear pathology does indeed process characteristic findings in electrocochleography and brainstem recording. Part of this study is also to see wheter these characteristic findings in retrocochlear pathology can be related to the localisation of the tumour process. Special attention will be given to the role of the efferent nervous system.

Chapter VI, VII

In these chapters the various parameters and recording techniques are outlined. The response to tone bursts stimuli of various frequencies are recorded by a round window electrode. Then the cerebello-pontine angle is exposed by a modified sub occipital apporach in which part of the cerebellum is sucked away.
A good view on the vestibular and cochlear nerve is obtained by this technique and selective experiments on each nerve are carried out. Three potentials are always recorded; cochlear microphonics, summating potential and compound action potential. In recording the whole nerve response three parameters were studied; the amplitude, the latency and the waveform of the recorded response.

Chapter VIII

In this chapter the experimental results are presented, which intended to mimic the effects produced by a tumour process in the cerebello-pontine angle. Selective experiments of nerve transection ad stretch are subsequently carried out on the vestibular and cochlear nerve. The experiments on the vestibular and cochlear nerve showed different results.
It was also found that contralateral ear was affected by (homolateral) stretch of the vestibular nerve.
The effects produced by experiments on the vestibular nerve could be possibly explained by changed activity of the efferent nerve system. The findings in cochlear nerve experiments could be due to a nerve conduction block or interference with the cochlear blood supply.
Additional experiments are required to study the possible role of efferent innervation.

Chapter IX

In this experimental section experiments are discussed which deal with the postulated influence of efferent nerve activity mediated by fibers passing alongside the vestibular nerve. Experiments which involve selective stretch of the vestibular nerve followed by transection of the crossed olivo-cochlear bundle and in reversed order are done to study the influence of efferent innervation.
These experiments confirm the postulated influence of increased efferent nerve activity with regard to the N_1-amplitude and the AP waveform. The results with respect to the cochlear potentials merely pointed to a reduced efferent activity after vestibular nerve stretch.
The postulated influence of efferent nerve activity was further evaluated by the use of a selective blocking agent of efferent nerve activity (Strychnine). It was demonstrated that all the effects produced by vestibular nerve stretch were to a large extent, restored by systemic application of this after selective stretch of the vestibular nerve.

Local blockade of efferent nervous activity was studied by application of KCl-solution on the vestibular nerve.
The results in homo- and contralateral recordings can be adequately explained by a block of inhibitory efferent influence. In order to see whether the afferent innervation is also affected by KCl application the recording of brainstem potentials is crucial.

Chapter X

The brainstem potentials are recorded by a bipolar electrode placed on the cerebal hemisphere and special attention is given to the peak-to-peak latency differences.
An increase of the peak I latency was confirmed, but no significant change between peak II, III and IV was found.
After selective stretch of the vestibular nerve the brainstem response lost its characteristic appearance, which did not allow a clear identification of peak V.
Administration of strychnine resulted in a restoration of the brainstem response.
Application of KCl on the vestibular nerve did not result in a complete block of afferent input, but the synchronous firing of the individual fibers was lost.

Chapter XI

In this chapter the experimental results of the various experiments are interpretated.
The results on the N_1-amplitude are explained by increased efferent nerve activity in the so called shunting model. The effects on the cochlear potentials are, however, not explained by this model. The neurapraxia phenomenon is introduced in this model. The neurapraxia phenomenon is introduced in this study which might occur after mechanical interference with a myelinated nerve. Since the efferent innervation of the cochlea consists of myelinated and unmyelinated nerve fibers it is postulated that these nerve fibers are affected in different ways by selective stretch of the vestibular nerve; stretch results in a conduction block of myelinated fibers (1), and increased activity of unmyelinated fibers (2). To explain the experimental results it is assumed that the myelinated efferent nerves mainly innervate the outer hair cells and the unmyelinated nerves mainly end on the afferent dendrites of the inner hair cells (3).
In this experimental model it is also necessary to assumethat the crossed efferent fibers mainly terminate on the outer hair cells while the uncrossed terminate on the inner hair cells (4).
The experimental results have been evaluated according to the proposed model. The various experiments are adequately explained by this theoretical model. The influence on the waveform of the recorded response is probably mediated through a change in ion conductance at the inner hair cells. Although the experimental results are satisfactory explained by this theoretical model the hypothesis on the distribution efferent innervation waits for further anatomical studies. The results of selective experiments on the cochlear nerve can be explained by a modification of the classic Keith-Lucas model.
The various studies on the simulation of effects produced by acoustic nerve tumours have all shown a characteristic response nerve tumors have all shown a characteristic response waveform. However in clinical studies of retrocochlear disorders normal AP waveforms have also been recorded.

XIII Samenvatting

Hoofdstuk I

Een algemene beschrijving van tumoren in de brughoek wordt hier gegeven met bijzondere aandacht voor tumoren van de achtste hersenzenuw. De klinische symptomen en de verschillende diagnostische onderzoekmethoden worden besproken. Een kort overzicht wordt gegeven van de chirugische methoden ter behandeling van deze tumoren.

Hoofdstuk II

Een experimenteel model wordt ontworpen om de effecten van tumoren van de nervus stato-acusticus na te bootsen. Er wordt hierbij vanuit gegaan dat genoemde tumoren symptomen veroorzaken ten gevolge van locale druk op de omgevende structuren. De mogelijk effecten van deze tumoren worden geanalyseerd aan de hand van selectieve rek en doorsnijdings experimenten van de nervus cochlearis en nervus vestibularis. Bij de cavia kunnen door de gescheiden beloop van deze zenuwen genoemde experimenten selectief worden uitgevoerd.

Hoofdstuk III

De anatomie van de brughoek bij het proefdier de cavia wordt besproken. Hierbij wordt speciale aandacht gegeven aan de efferente innervatie van de cochlea.
De efferente vezels verlopen via de nervus vestibularis en hebben een verschillend verloop en synaps met binnenste en buitenste haarcellen.

Hoofdstuk IV

De betekenis van de efferente innervatie van de cochlea wordt nagegaan aan de hand van verschillende experimenten.
Electrische stimulatie van het efferente systeem heeft een inhiberend effect op de afferente input. Deze inhiberende invloed wordt bevestigd in doorsnijdings experimenten. Acetylcholine is vermoedelijk de transmitter stof van het efferente systeem. Ofschoon verschillende effecten aan de invloed van het efferente systeem zijn toegeschreven, is de functionele betekenis nog onbekend.

Hoofdstuk V

In dit hoofdstuk worden de experimenten omschreven en gemotiveerd, met betrekking tot het onderzoek van retrocochleaire pathologie. Het doel van deze experimenten is na te gaan of bepaalde retrocochleaire lesies specifieke verandering geven in de parameters welke in de electrocochleografie en registratie van hersenstampotentialen worden afgeleid. Speciale aandacht wordt hierbij gegeven aan de rol van het efferente systeem.

Hoofdstuk VI, VII

In deze hoofdstukken wordt de techniek besproken waarmee de potentialen worden afgeleid en de cochlea gestimuleerd. Speciale aandacht wordt gegeven aan de techniek van de zgn. smalle band AP. De chirurgische benadering van de brughoek bij de cavia wordt besproken.
In hoofdstuk VII worden de verschillende parameters gedefinieerd en toegelicht.
Steeds worden 3 potentialen geregistreerd, cochleaire microphonie, sommatie potentiaal en de samengestelde actie potentiaal.
Van de samengestelde actie potentiaal werden de latentie, de amplitude en de golfvorm geanalyseerd.

Hoofdstuk VIII

In dit hoofdstuk worden de experimentele resultaten besproken die de verschijnselen van een tumor in de brughoek nabij komen. Selectieve experimenten van rek en doorsnijding worden uitgevoerd, zowel van de nervus cochlearis als de nervus vestibularis. De experimenten van de nervus cochlearis en de nervus vestibularis geven verschillende resultaten. Bovendien werd vastgesteld dat bij homolaterale rek van de nervus vestibularis de parameters afgeleid van het contralateralé oor beïnvloed werden. Deze veranderingen worden mogelijk verklaard door een verandering in de activiteit van het efferente systeem.

Hoofdstuk IX

In dit hoofdstuk worden nadere experimenten verricht om de invloed van het efferente systeem te onderzoeken.
Hiertoe werd selective doorsnijding van het gekruiste efferente systeem uitgevoerd in combinatie met rek van de nervus vestibularis. Deze experimenten bevestigen de veronderstelde invloed van het efferente systeem met betrekking tot de amplitude en de golfvorm van de actie potentiaal. Voor de cochleaire potentialen werd geen bevestiging gevonden.
De efferente activiteit werd verder onderzocht met behulp van selectieve blokkerende stoffen als Strychnine. Locale blokkade van het efferente systeem werd verkregen door applicatie van een KCl oplossing.
Ook deze experimenten bevestigen de inhiberende invloed van het efferente systeem op de afferente vezels.

Hoofdstuk X

De potentialen van de hersenstam worden afgeleid met behulp van een bipolaire electrode. In de gemeten response is naast de golfvorm vooral de latentie tussen de verschillende golven van belang.
De latentie toename van de eerste golf werd bevestigd, terwijl er geen significante latentie verschillen werden gevonden tussen golf II, III en IV. Na selectieve rek van de n. vestibularis verliest de response zijn karakteristieke vorm waardoor identificatie van golf V niet mogelijk is. Wanneer strychnine werd toegediend herstelt de golfvorm zich.

Hoofdstuk XI

De resultaten van de verschillende experimenten worden hierin bijeen gebracht. Het effect op de amplitude van N_1 worden verklaard door een toename van de efferente activiteit volgens het zgn. shunting model. De effecten op de cochleaire potentialen worden niet met dit model verklaard.
Het neurapraxie verschijnsel wordt besproken.
In het nieuwe theoretische model wordt verondersteld dat de cochlea geinnerveerd wordt door gemyeliniseerde en ongemyeliniseerde vezels en dat deze vezels verschillend reageren op mechanische stimuli.
Tenslotte wordt veronderstelt dat de gekruiste efferente vezels eindigen op de buitenste haarcellen terwijl de ongekruiste vezels de binnenste haarcellen innerveren.
De experimentele resultaten worden geëvalueerd aan de hand van dit theoretische model. Daarbij blijkt dat de gevonden resultaten goed aansluiten bij het voorgestelde model. Aanvullend anatomisch onderzoek zal daarbij in de toekomst moeten leren of dit veronderstelde innervatie patroon inderdaad aanwezig is.
De experimenten die betrekking hebben op de n. cochlearis kunnen verklaard worden door middel van een modificatie van het Keith-Lucas model.
De verschillende experimenten die beoogden de effecten van retrocochleaire processen te onderzoeken toonden steeds een karakteristieke verandering van de golfvorm. Deze karakteristieke golfvorm wordt eveneens gezien bij de klinische studies van retrocochleaire lesies. Echter in een aantal gevallen is ook aan normale golfvorm gevonden.
Aangezien de andere parameters in dit klinisch onderzoek niet bekend zijn, kunnen deze niet worden gebruikt als criteria bij de diagnostiek van retrocochleaire processen.

XIV References

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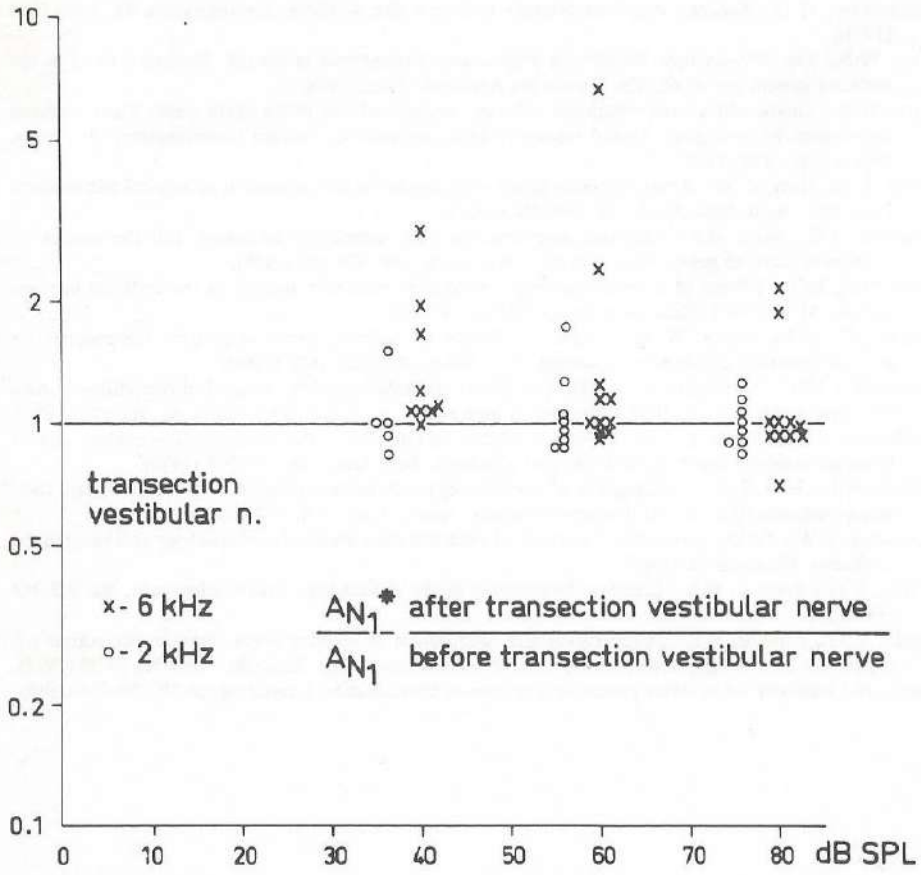


Fig. 1 The N_1-amplitude ratio has been calculated, at 40, 60 and 80 dB SPL, before (A_{N_1}) and after ($A^{*}_{N_1}$) vestibular nerve transection in 11 experiments at 2 and 6 kHz.

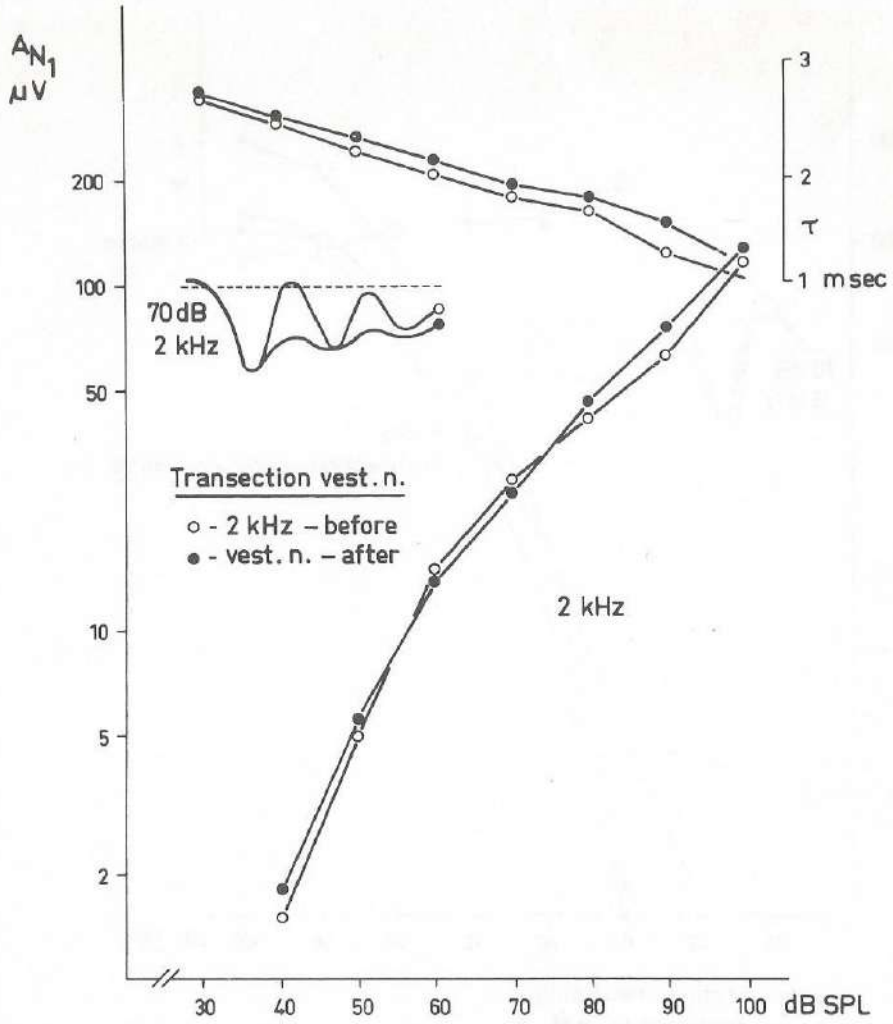


Fig. 2 The amplitude-intensity curve for 2 kHz tone burst stimulation (scale on the left hand side) shows a range of 2-200 μV for a change in intensity of 40-100 dB SPL. There is no change after vestibular nerve section. The latency-intensity curve (scale on the upper right-hand side) shows a change from 1 to 3 msec for the indicated intensity range; immediately after vestibular nerve section the latencies are slightly increased. The AP-waveform at 70 dB SPL (see insert) shows a change to a monophasic broad waveform after transection of the vestibular nerve.

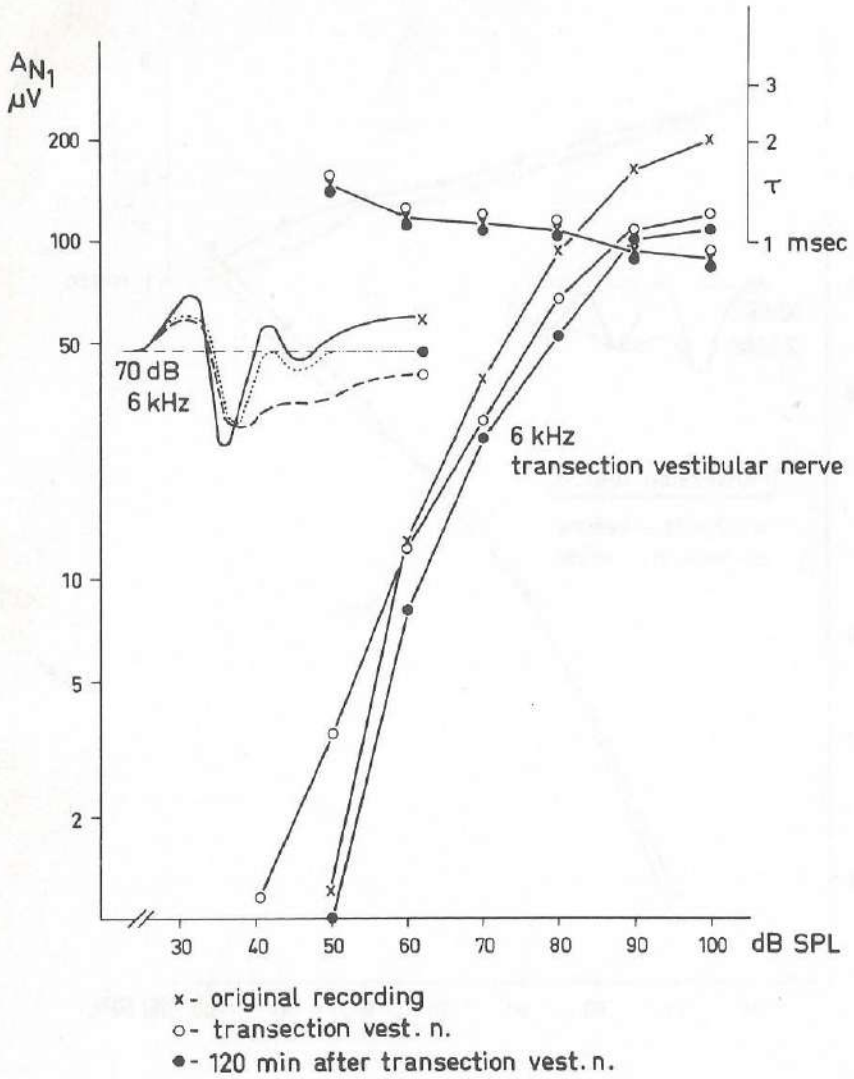


Fig. 3 The I/O-curve at 6 kHz illustrates a slight N_1-amplitude increase at the lower intensities after vestibular nerve section and a N_1-amplitude reduction at higher intensities. Two hours after vestibular nerve transection the AP wave showed a tendancy to restore to normal .

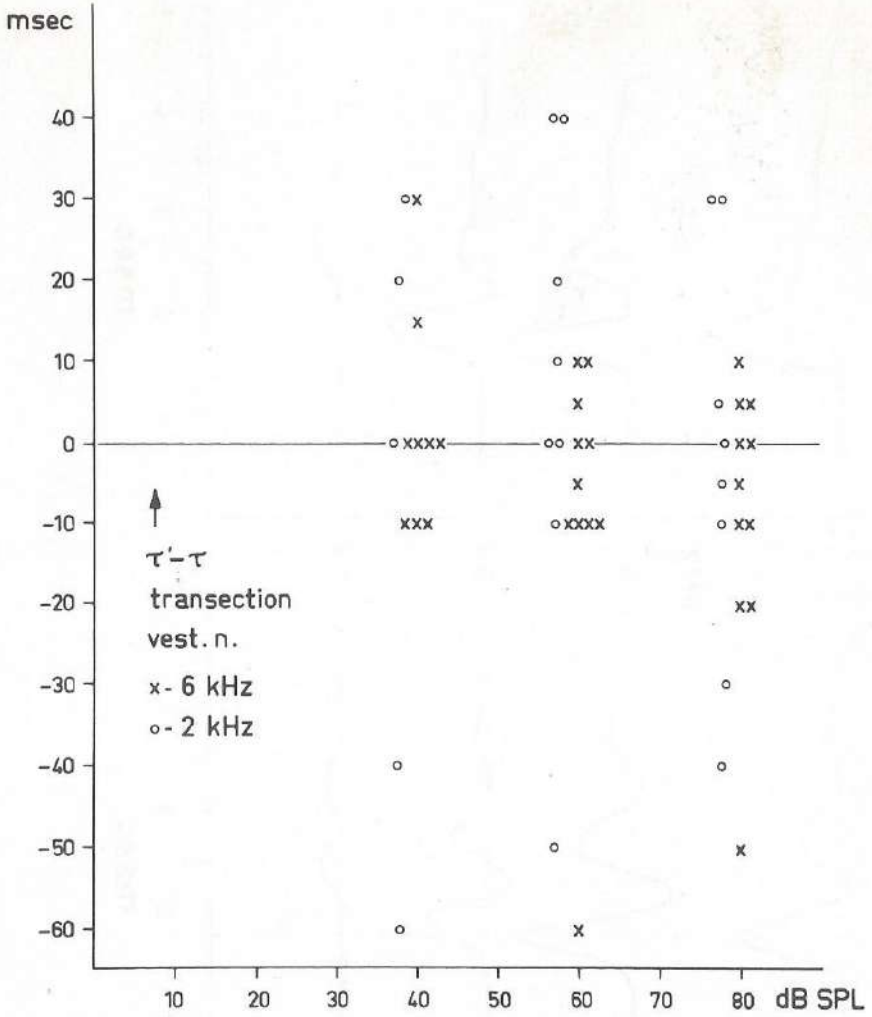


Fig. 4 At 2 and 6 kHz the N_1-latency difference is shown in eleven experiments after vestibular nerve section.

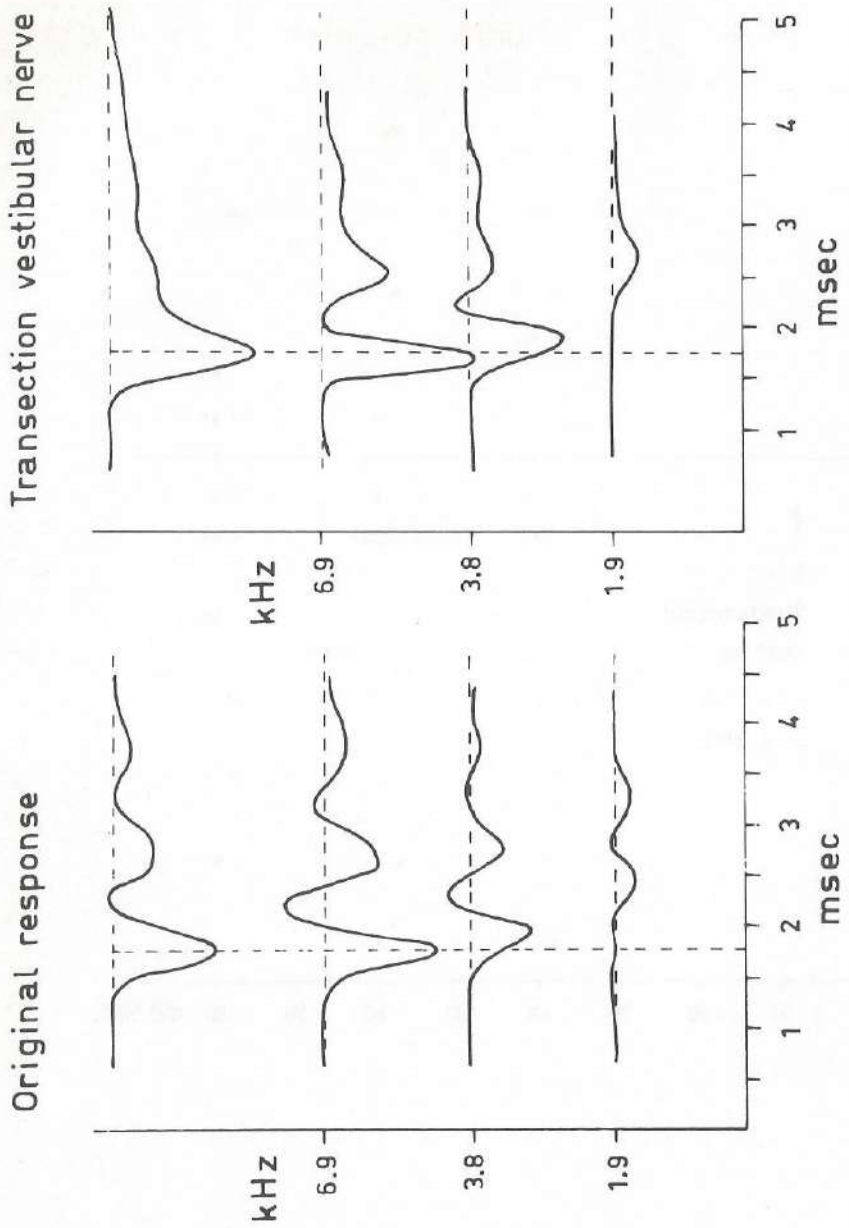


Fig. 5 This illustration shows the narrow-band action potentials before and after vestibular nerve transection. The positive peak (P_1) is markedly reduced (6.9 kHz).

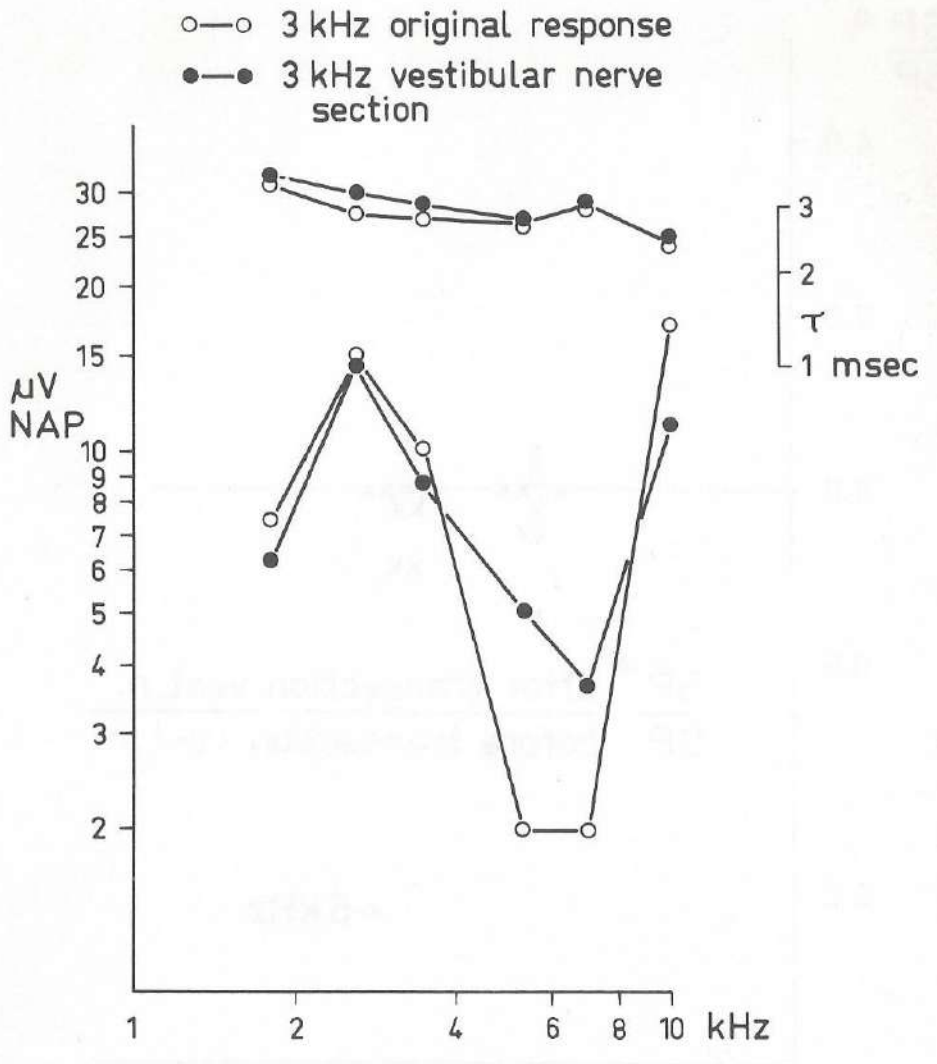


Fig. 6 The narrow-band amplitudes before and after vestibular nerve transection have been calculated showing an amplitude increase at 4-9 kHz.

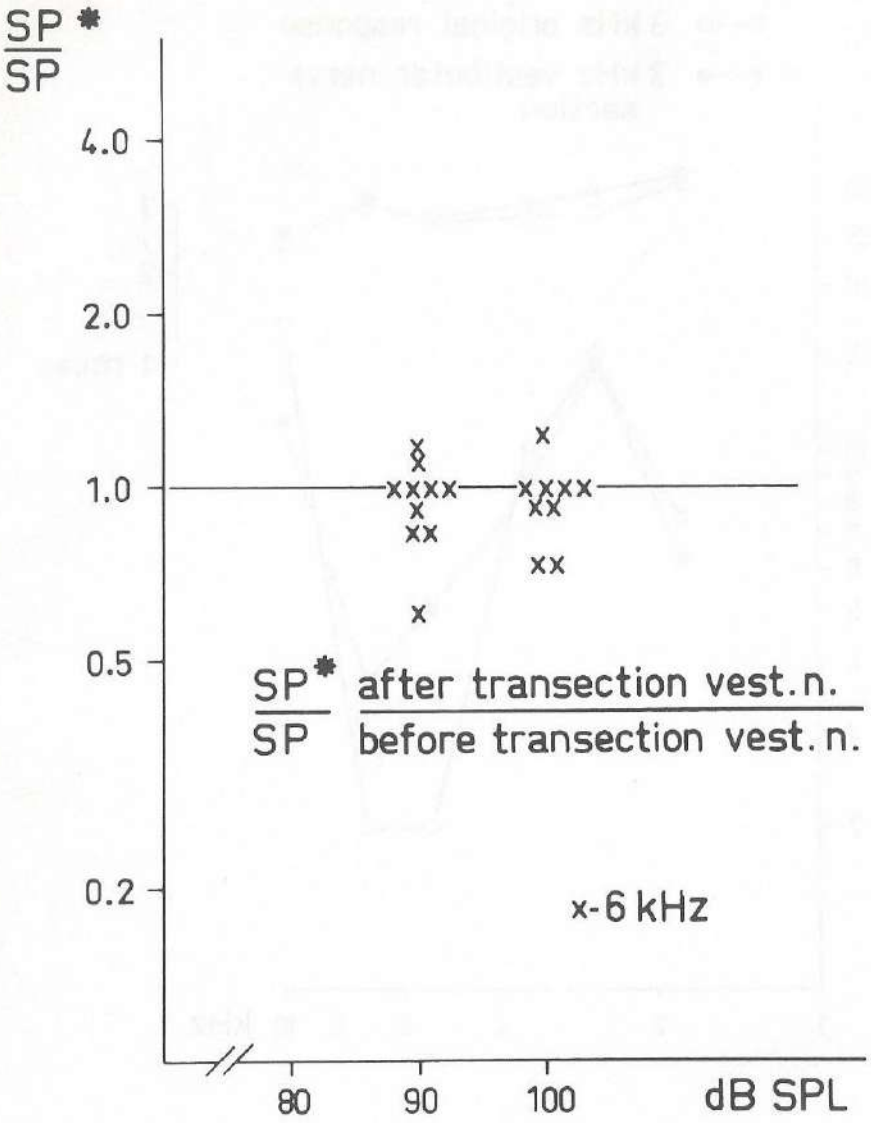


Fig. 7 The SP-amplitude ratio has been calculated at 90 and 100 dB SPL, before (SP) and after SP*) transection of the vestibular nerve, and showed no statistical significance from 1.

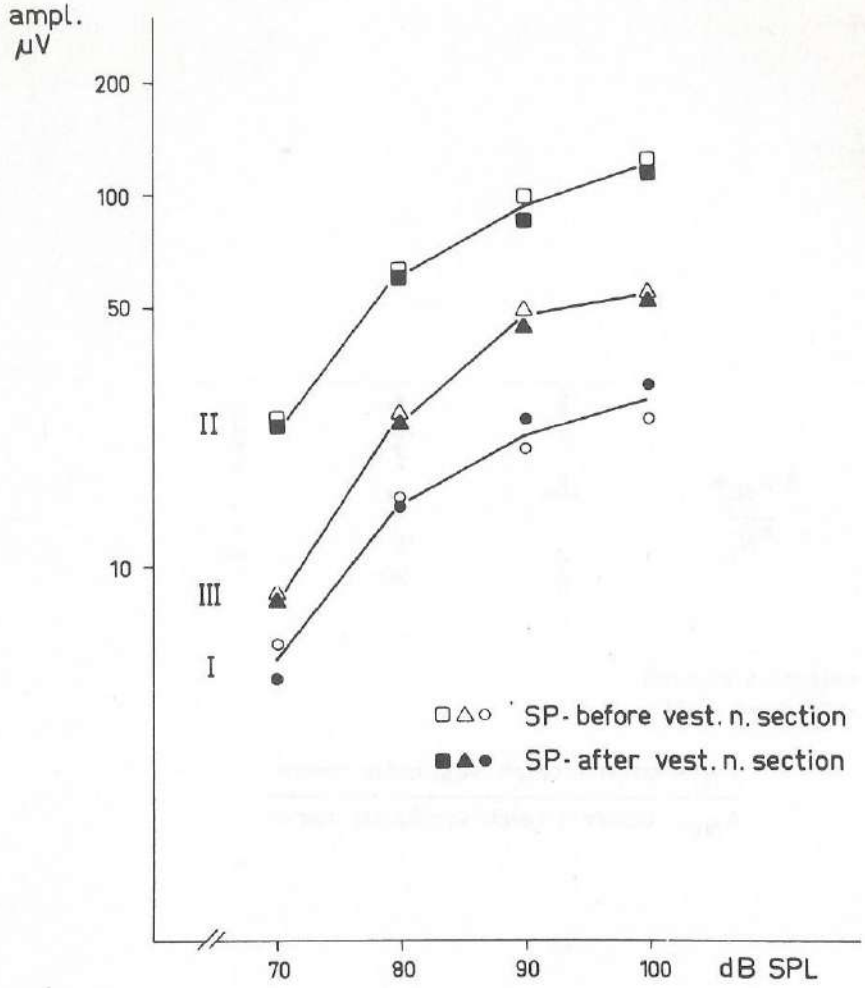


Fig. 8 The SP-amplitude ratio at 70, 80, 90 and 100 dB SPL is calculated in three experiments. The SP-amplitude was not changed by vestibular nerve transection.

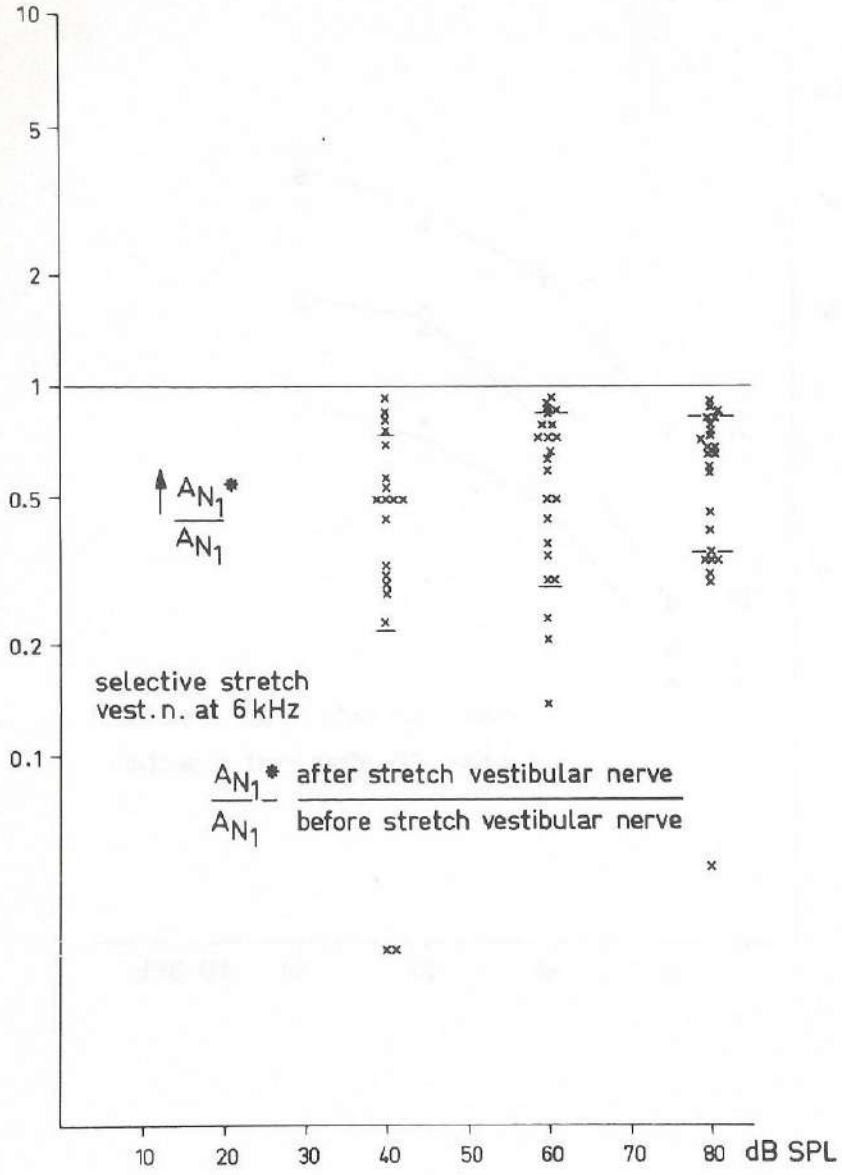


Fig. 9 The A_1-amplitude ratio has been calculated at 40, 60 and 80 dB SPL, before (A_{N_1}) and after ($A_{N_1}^*$) selective stretch of the vestibular nerve in experiments at 6 kHz. At all frequencies a marked N_1-amplitude reduction was found after vestibular nerve stretch. (– = standard deviation).

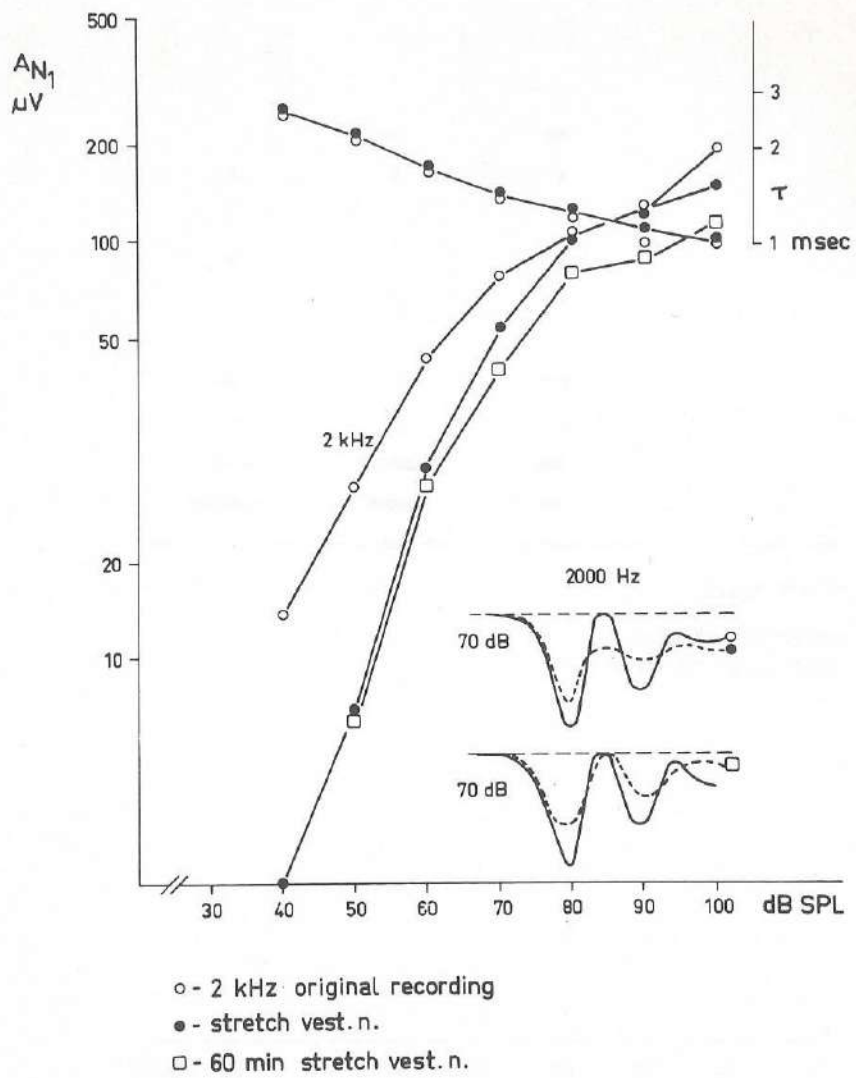


Fig. 10 In I/O curve at 2 kHz in an individual experiment shows a marked A_{N_1}-amplitude reduction after vestibular nerve stretch. The AP-waveform at 2 kHz shows a characteristic cleft distortion. After 60 min. the N_1-amplitude at high intensities is even further reduced but the AP-waveform shows a tendency to restore to the original response at 70 dB SPL.

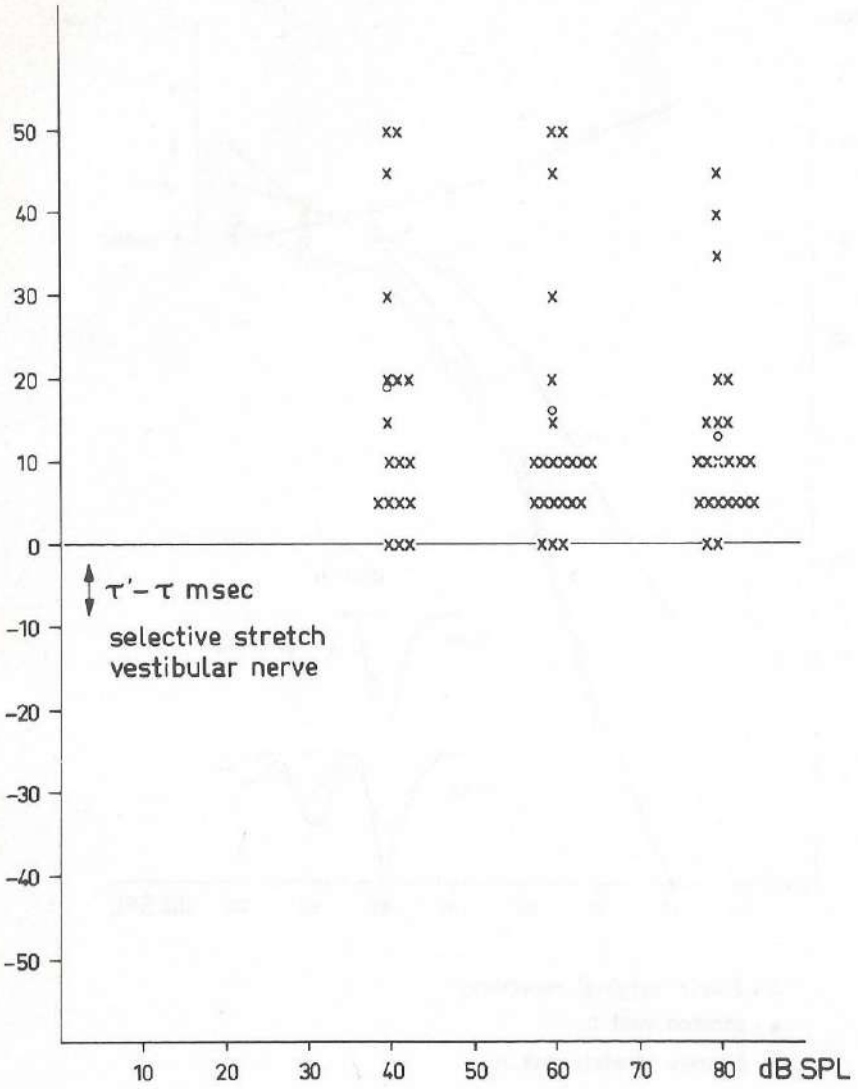


Fig. 11 At 6 kHz the N_1-latency difference (T^1-T) is calculated before and after vestibular nerve stretch. At all frequencies the N_1-latency did increase.

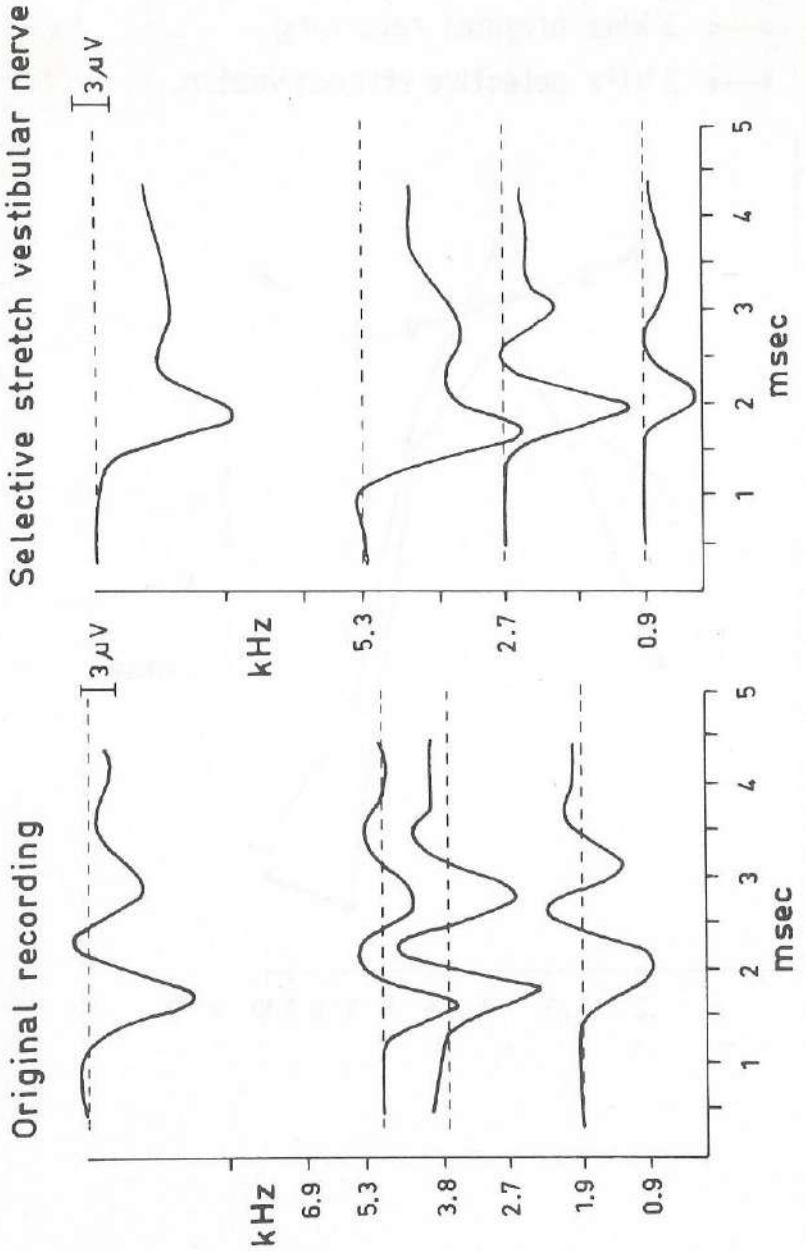


Fig. 12 This figure shows the narrow-band contributions at various frequencies. After stretch of the vestibular nerve the narrow-band AP-waveform becomes monophasic (5.3 kHz).

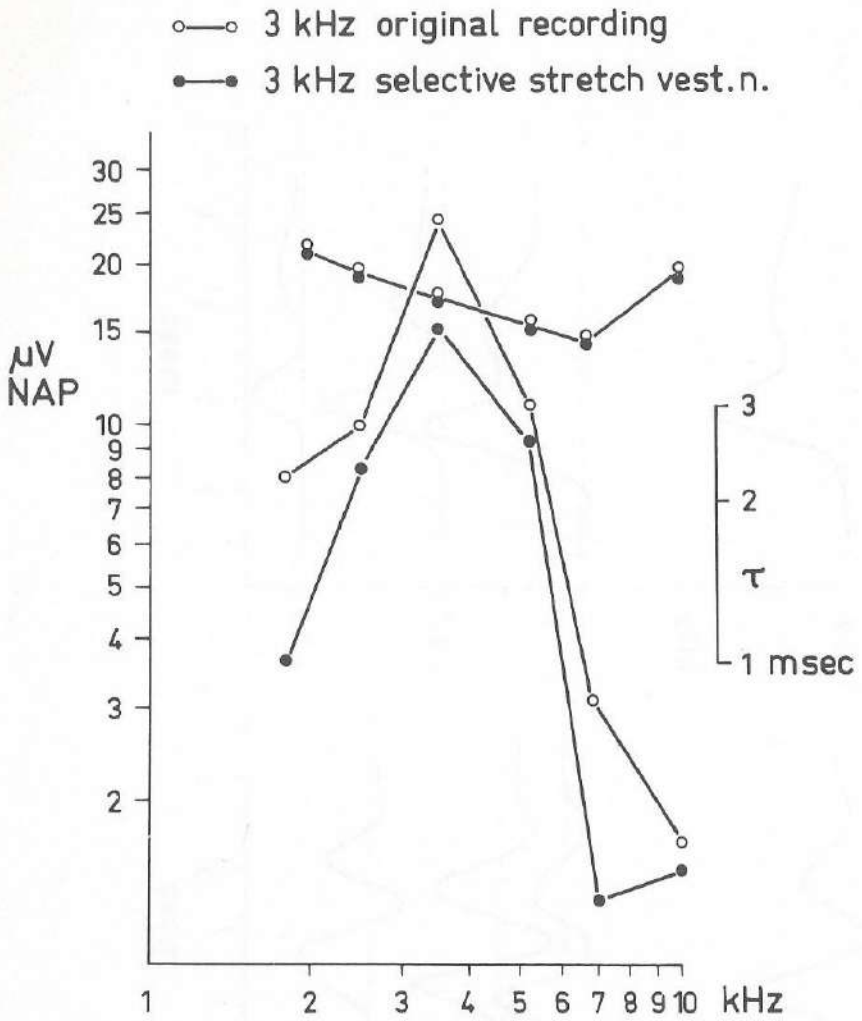


Fig. 13 The narrow-band N_1-amplitudes before and after vestibular nerve stretch have been calculated and show an overall amplitude reduction.

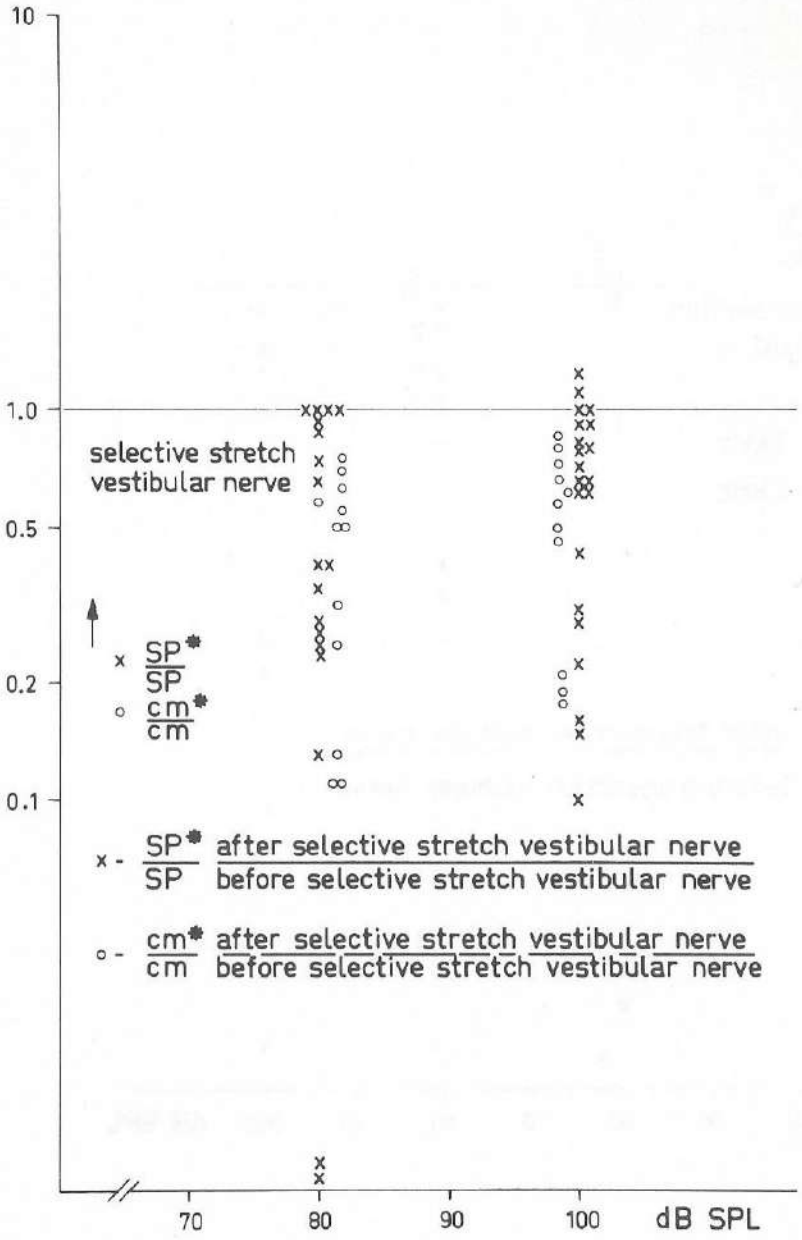


Fig. 14 The SP-amplitude ratio at 80 and 100 dB SPL before (SP) and after (SP*) stretch of the vestibular nerve has been determinated. At both frequencies the SP-amplitude after vestibular nerve stretch is reduced. The CM ratio shows the same pattern.

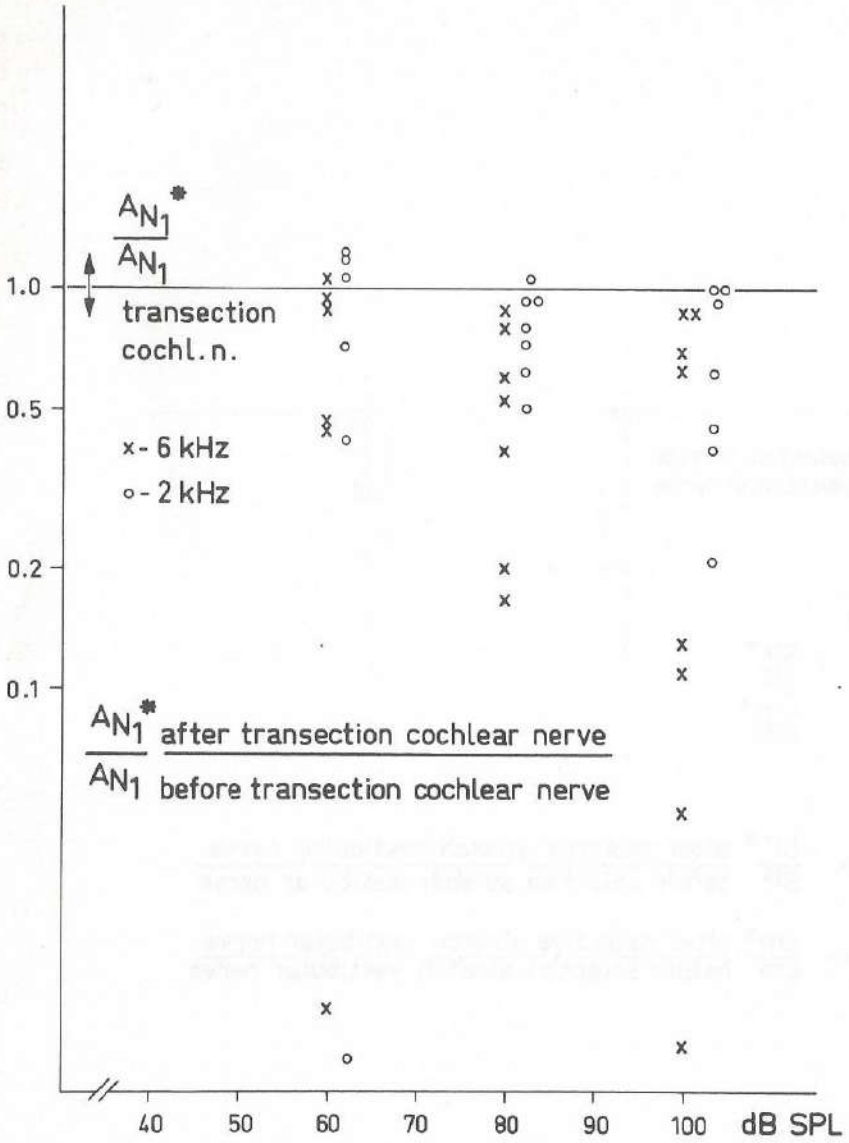


Fig. 15 In 8 animals the N_1-amplitude ratio before (A_{N_1}) and after cochlear nerve transection ($A^*_{N_1}$) has been calculated at 2 and 6 kHz. A significant A_{N_1} reduction was found after cochlear nerve transection.

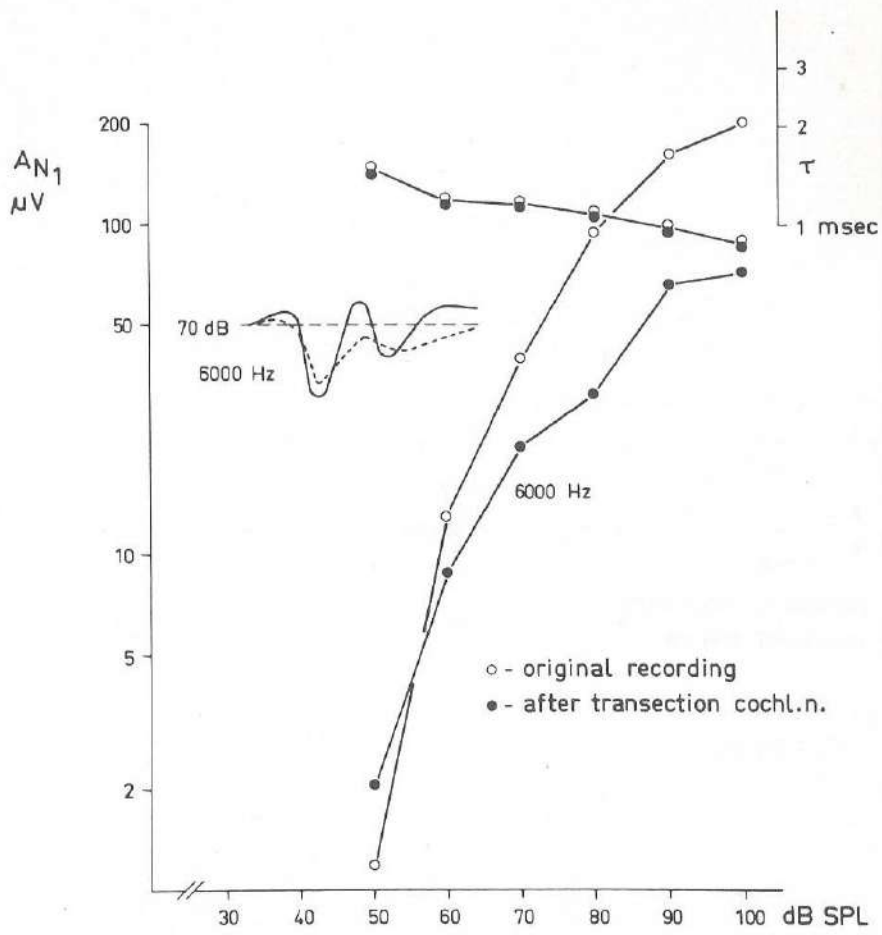


Fig. 16 The I/O-curve in an individual experiment at 6 kHz demonstrates a marked N_1-amplitude reduction after partial transection of the cochlear nerve. At 70 dB SPL the AP-waveform has a monophasic appearance.

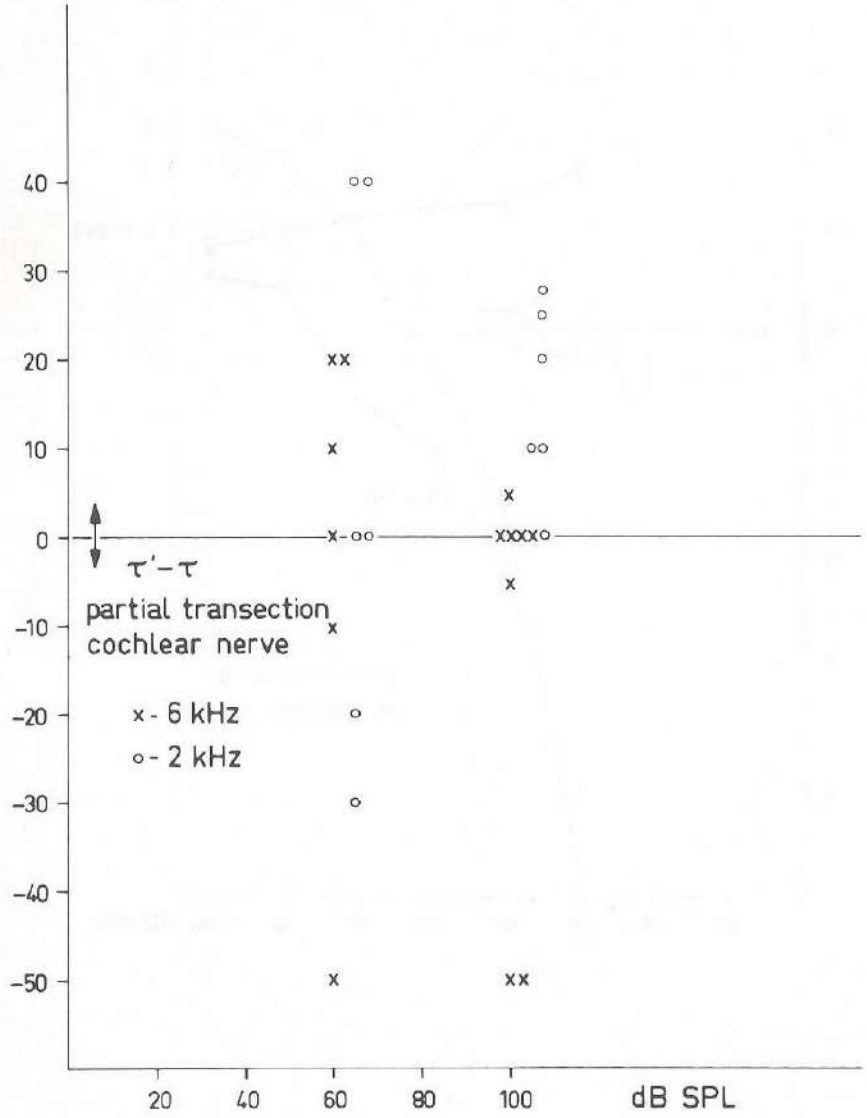


Fig. 17 The effect on the N_1-latency at 6 kHz shows a decrease at 60 and 100 dB SPL. At the same intensities the latency is increased at 2 kHz.

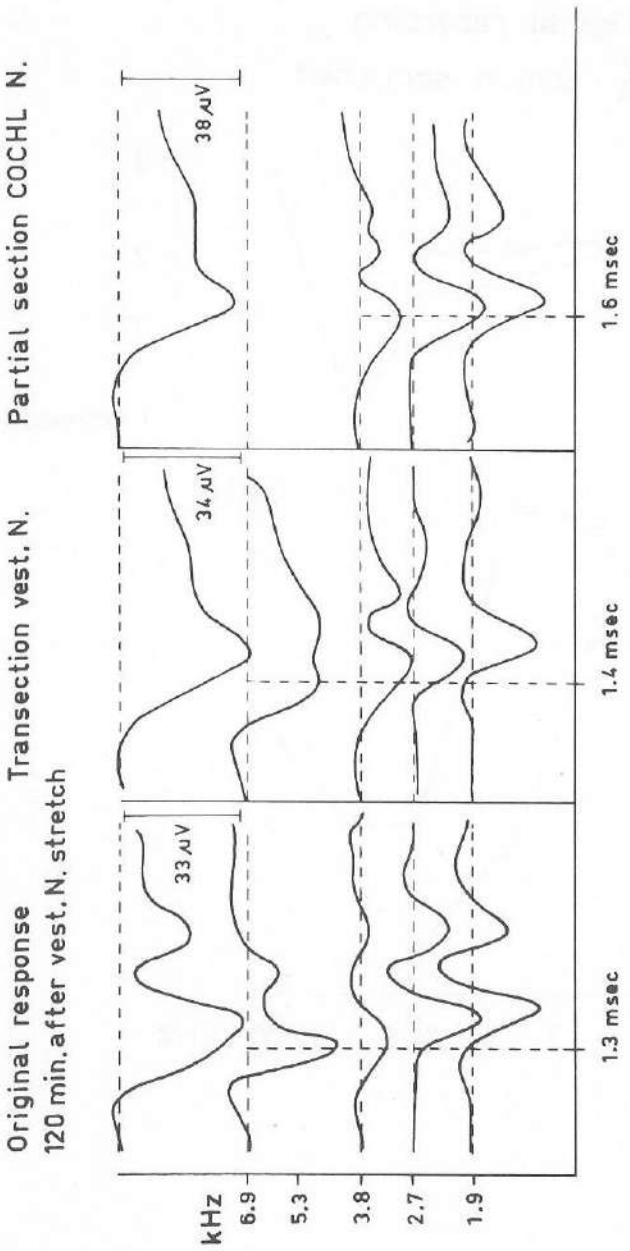


Fig. 18 The AP-waveform after vestibular nerve stretch followed by partial section of the cochlear nerve shows that the AP-waveform remains monophasic.

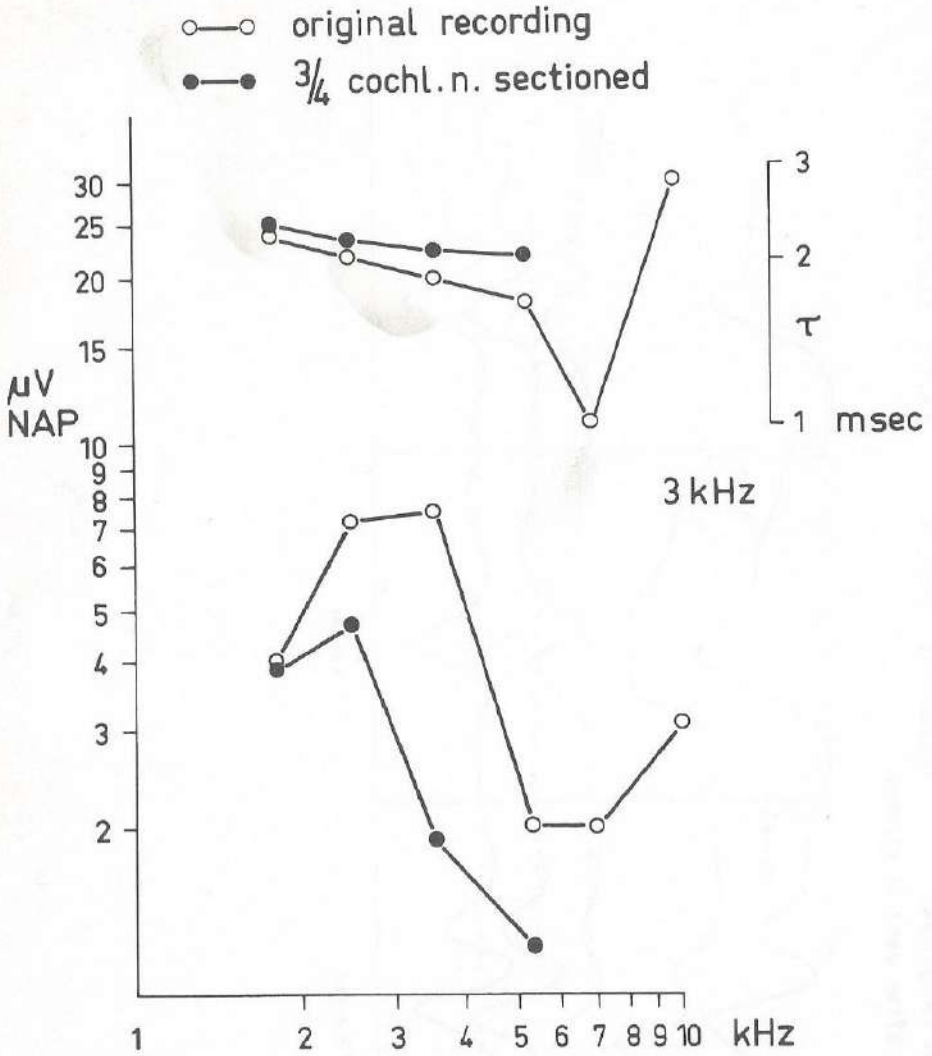


Fig. 19 This illustration shows the NAP amplitudes after cochlear nerve section. The amplitude reduction occurs mainly at the higher central frequencies.

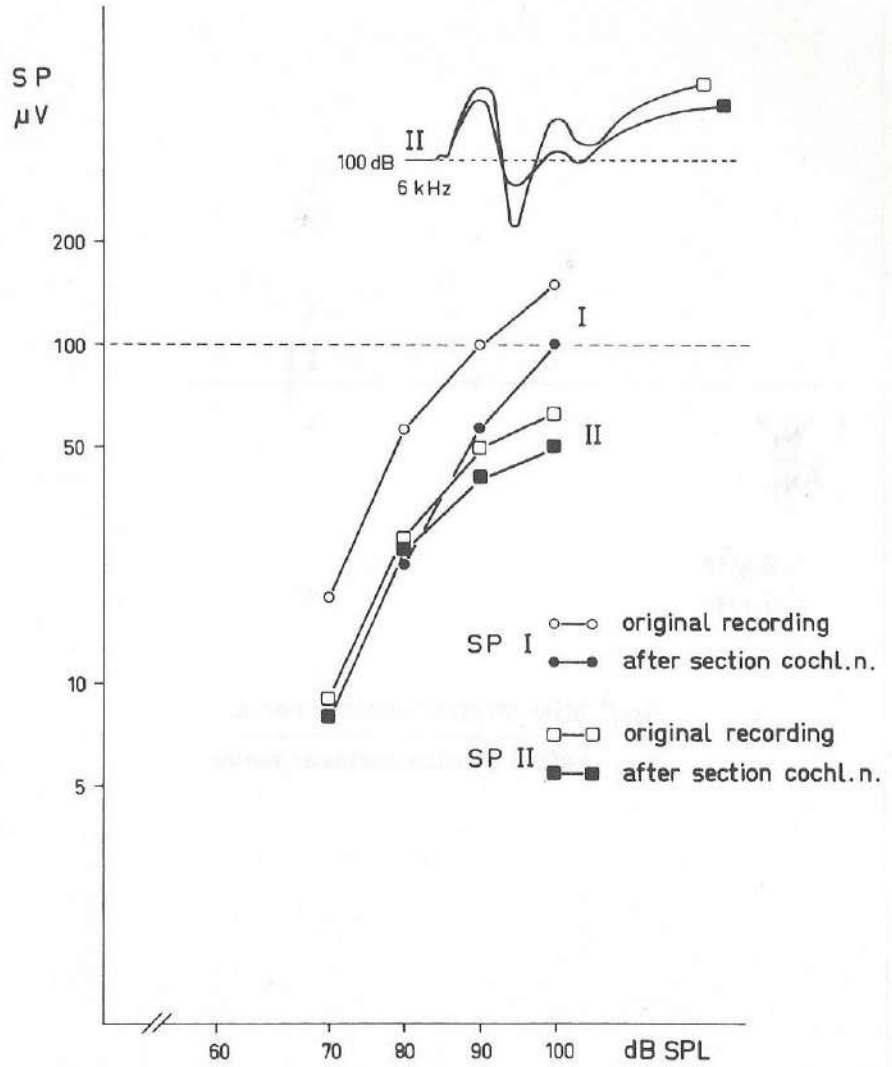


Fig. 20 In 2 experiments the SP-amplitudes before and after partial cochlear nerve transection are shown, demonstrating a SP-amplitude reduction after cochlear nerve section.

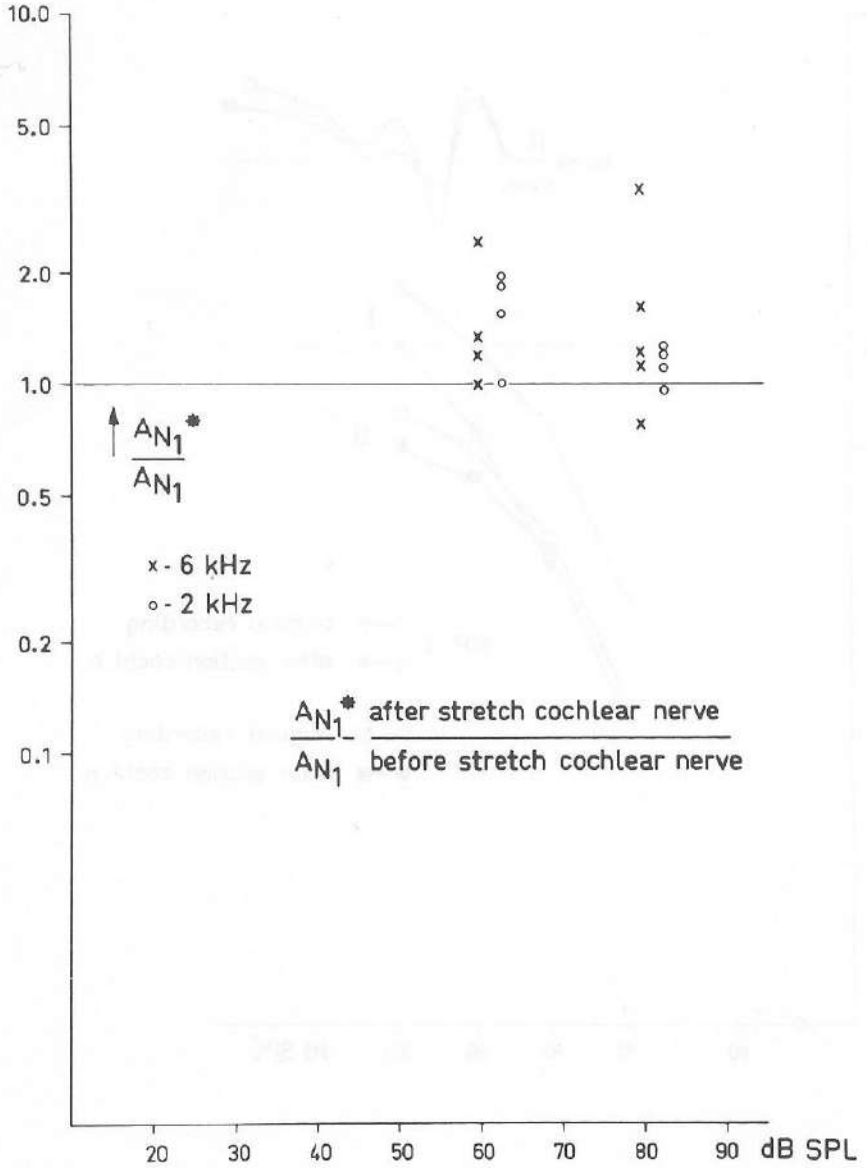


Fig. 21 This figure demonstrates the N_1-amplitude ratio before (A_{N_1}) and after $A_{N_1}^*$) selective stretch of the cochlear nerve in 5 experiments at 2 and 6 kHz. The N_1-amplitude increased after cochlear nerve stretch.

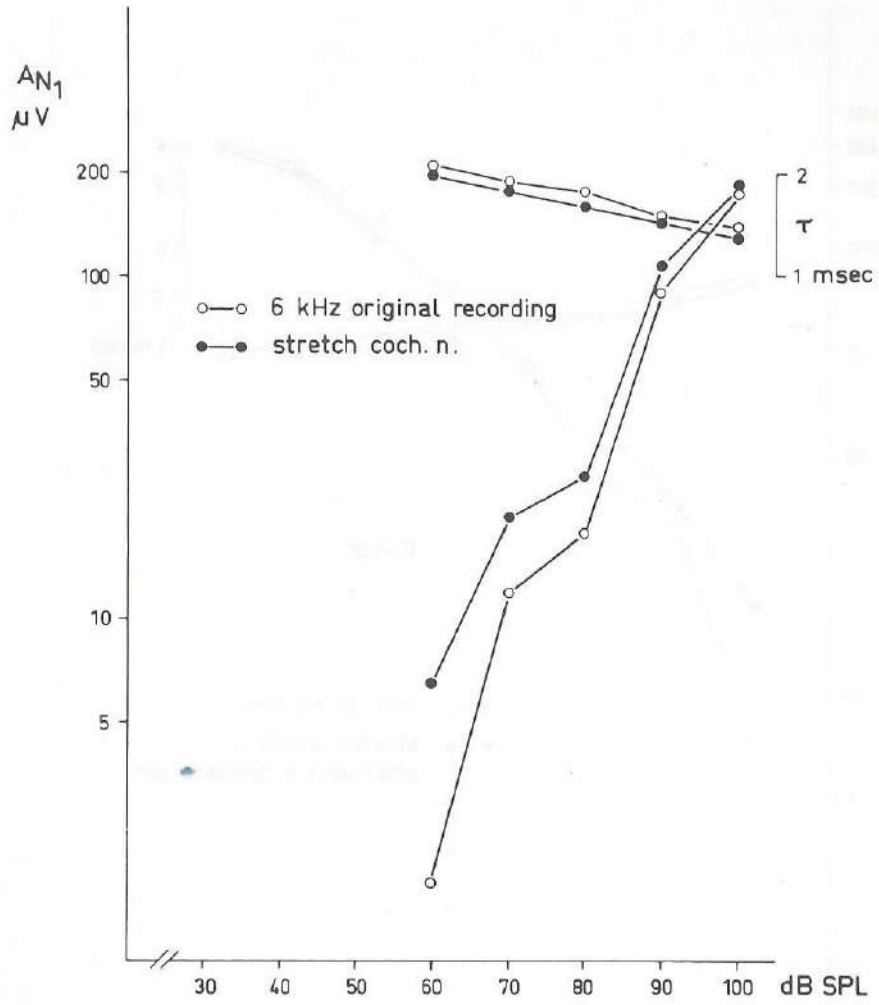


Fig. 22 The I/O-curve at 6 kHz before and after cochlear nerve stretch shows an amplitude increase at the lower intensities.

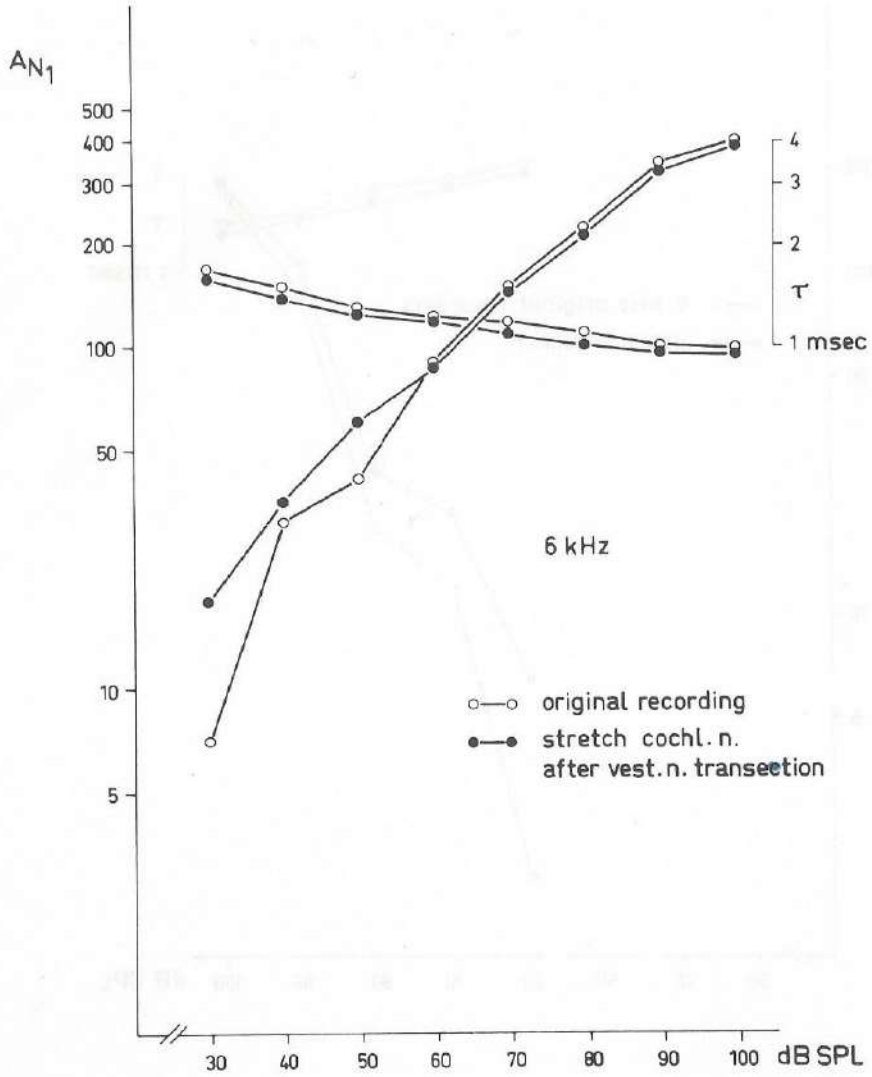


Fig. 23 In this experiment stretch is applied to the cochlear nerve after transection of the vestibular nerve. A moderate amplitude increase does occur at the lower intensities.

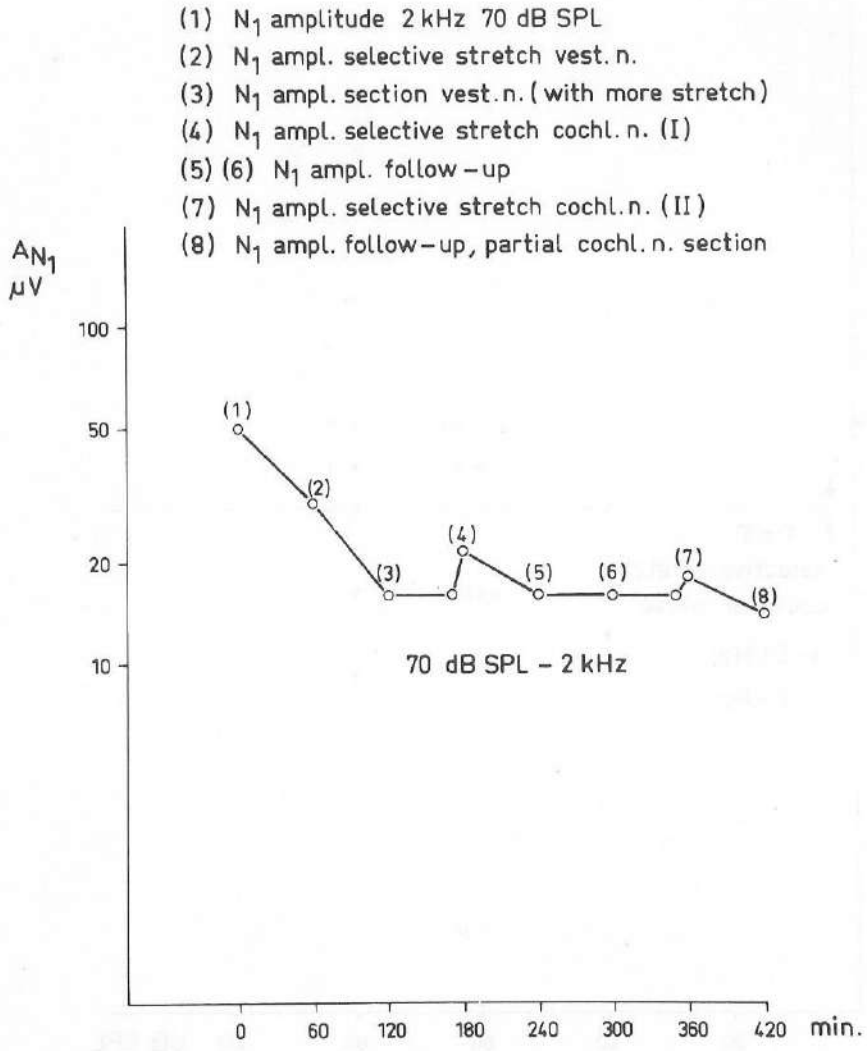


Fig. 24 This illustration shows a series of experiments at 2 kHz. Stretch of the vestibular nerve results in a marked N_1-amplitude reduction (2).
When stretch is applied to the cochlear nerve the N_1-amplitude does increase (4) (7).
Transection of the cochlear nerve results in an amplitude reduction (8).

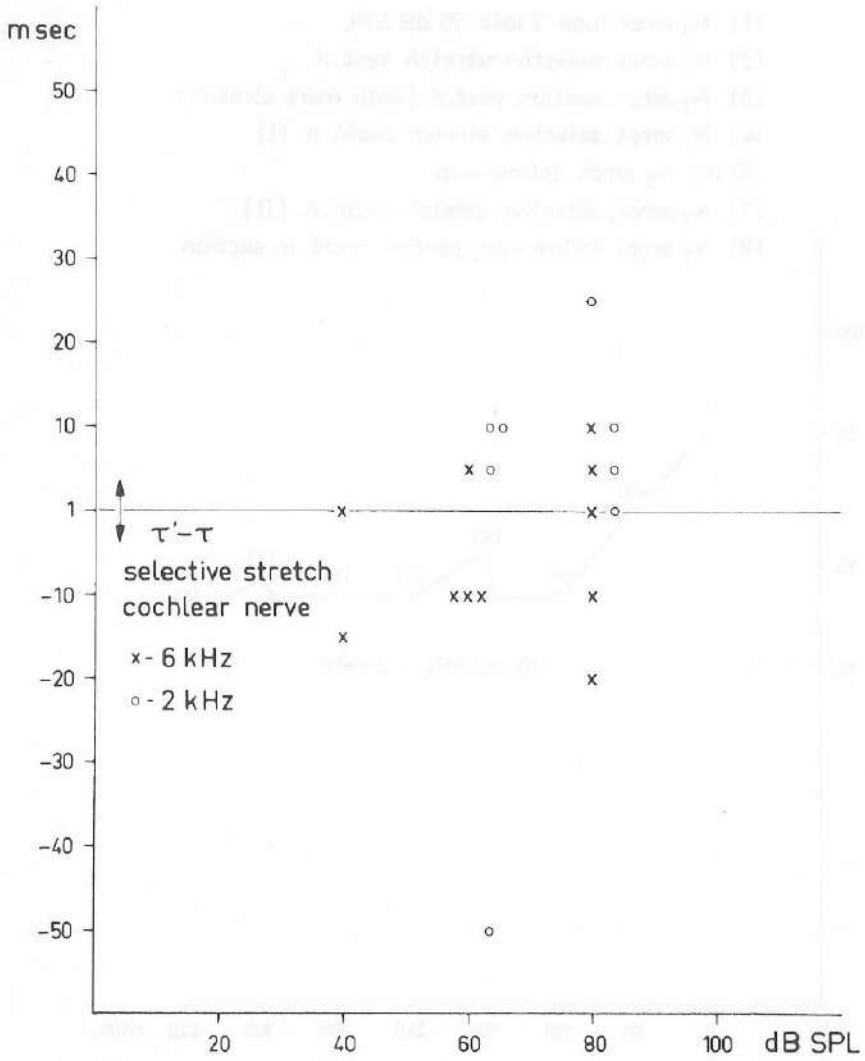


Fig. 25 The effects of cochlear nerve stretch on the N_1-latency is demonstrated in this figure. At high intensities at 6 kHz there is a slight increase while at low intensities the latency is reduced.

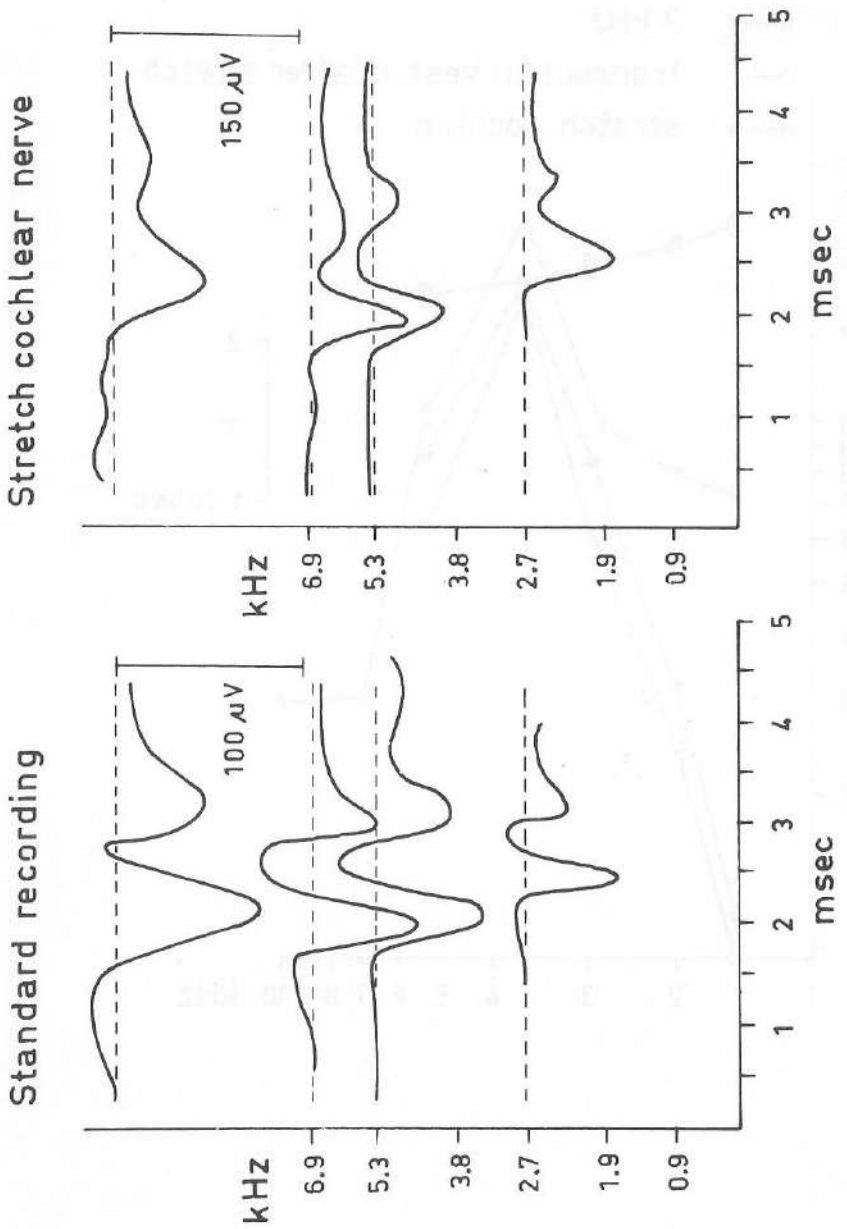


Fig. 26 The AP-waveform demonstrates a monophasic appearance after stretch of the cochlear nerve.

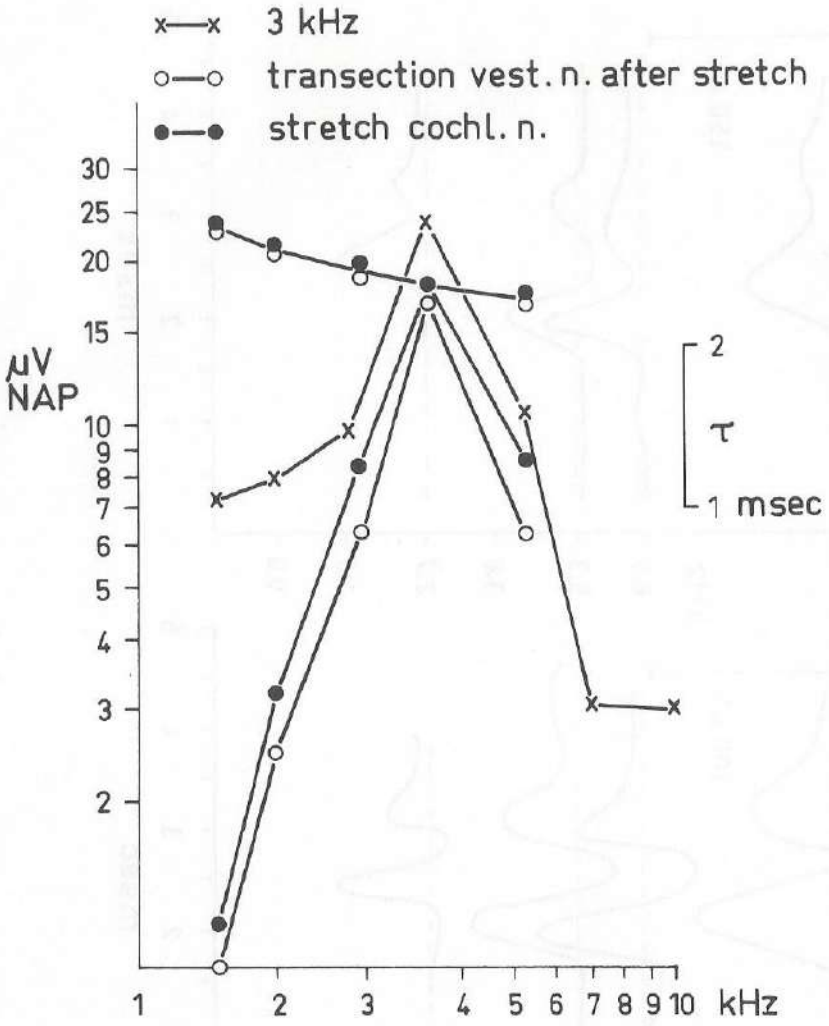


Fig. 27 The NAP-amplitude shows a slight increase after vestibular nerve transection.

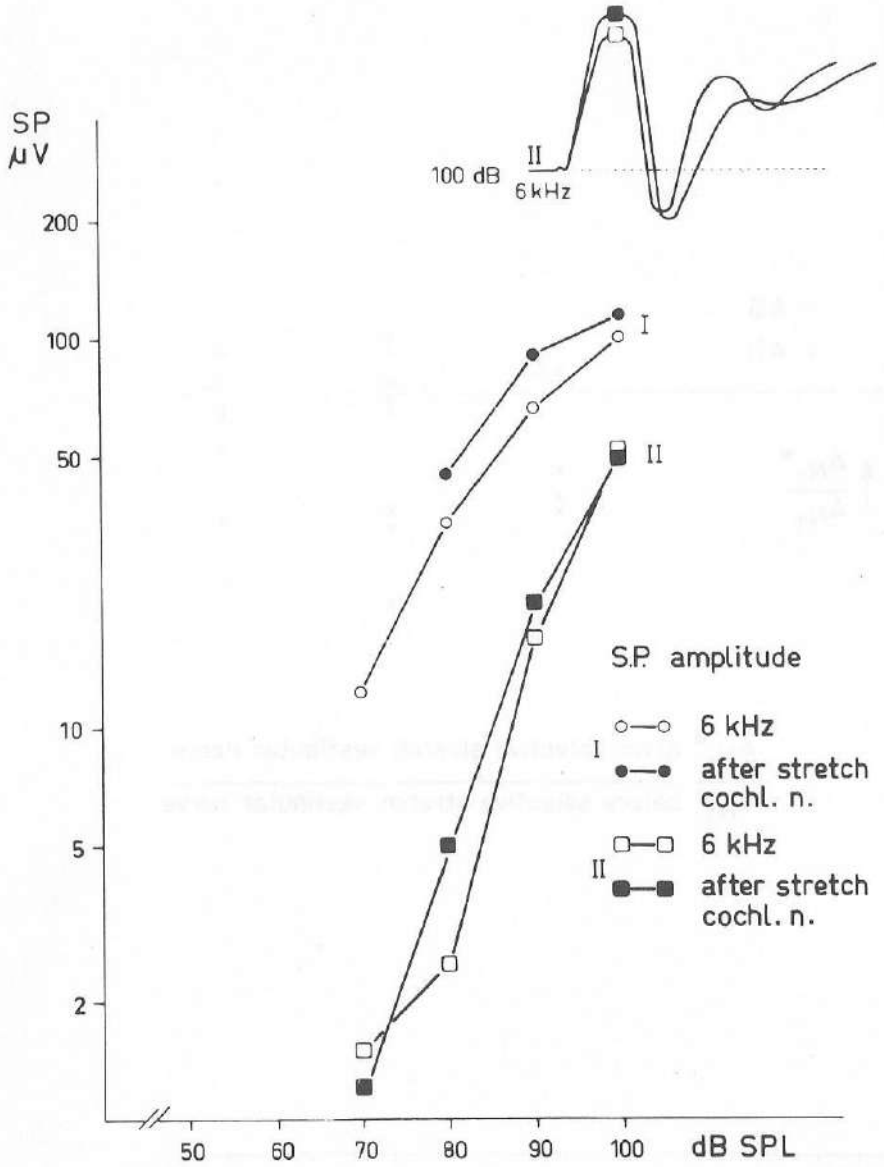


Fig. 28 The SP-amplitude in 2 experiments at 6 kHz is demonstrated after stretch of the cochlear nerve. A slight increase is observed in these experiments.

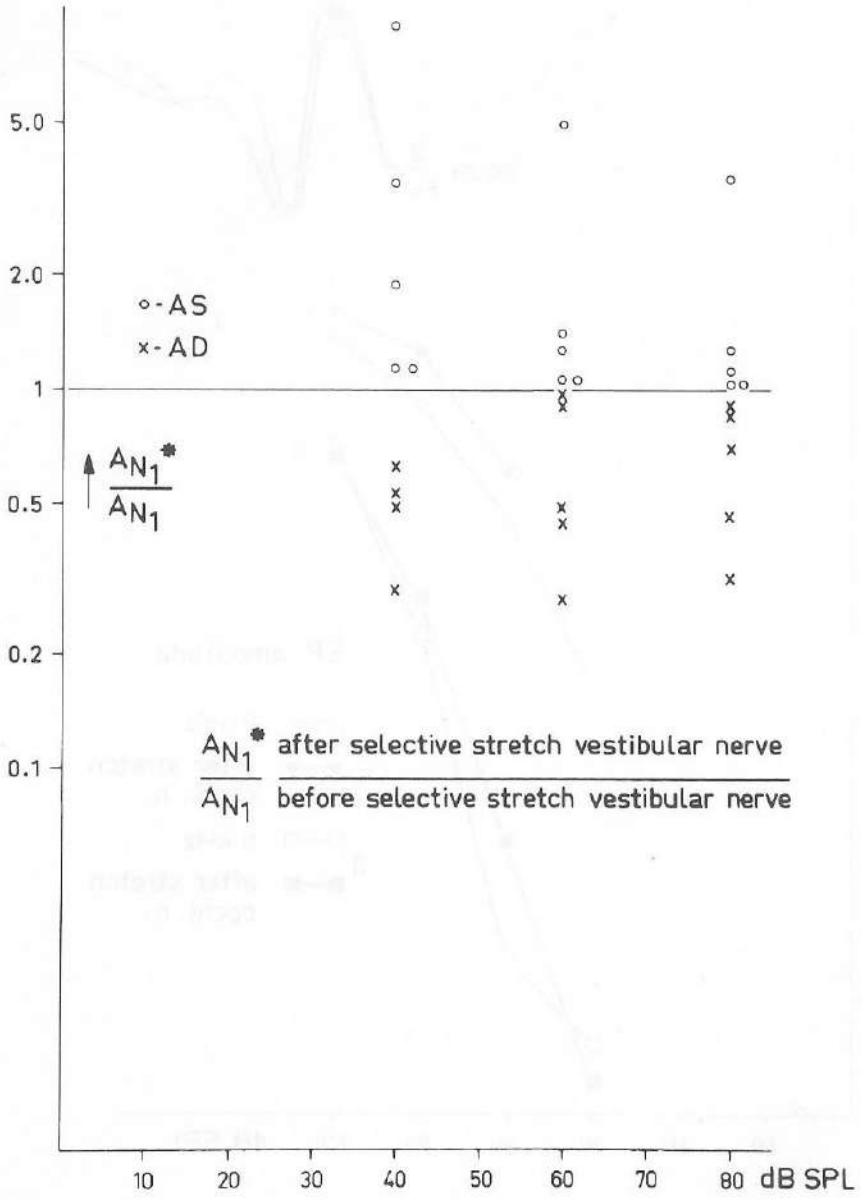


Fig. 29 This illustration shows the effect on the N_1-amplitude after homolateral (AD) stretch of the vestibular nerve in bilateral recordings.
The homolateral N_1-amplitude is reduced while the contralateral N_1-amplitude (AS) is increased.

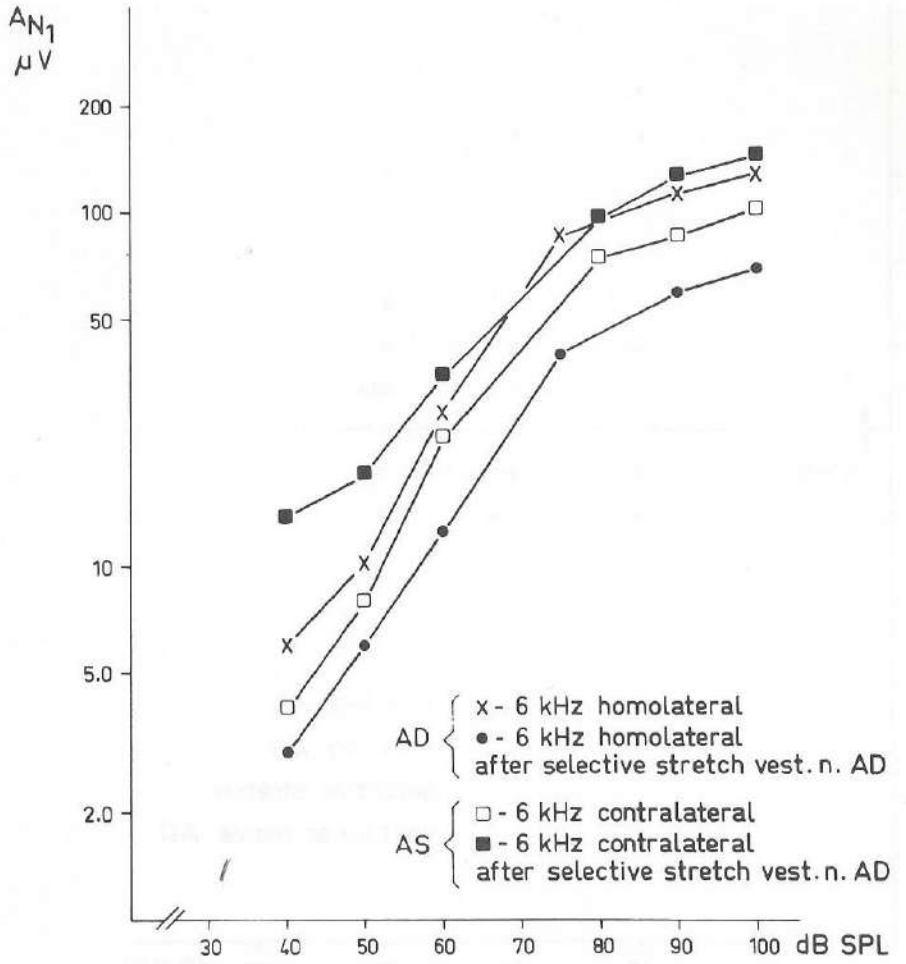


Fig. 30 The I/O-curves demonstrate the effect on the N_1-amplitude after homolateral stretch in bilateral recording at 6 kHz.

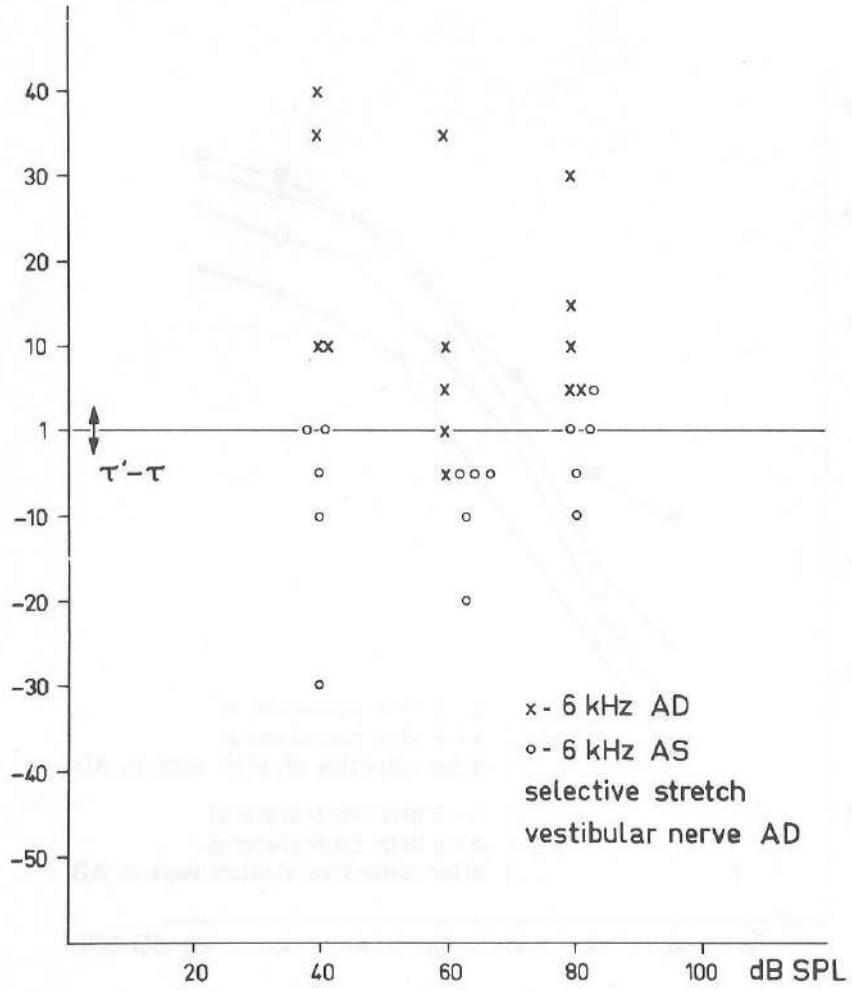


Fig. 31 In this illustration it is shown that the homolateral latency increase of homolateral (AD) stretch of the vestibular nerve is accompagnied by a contralateral (AS) latency reduction.

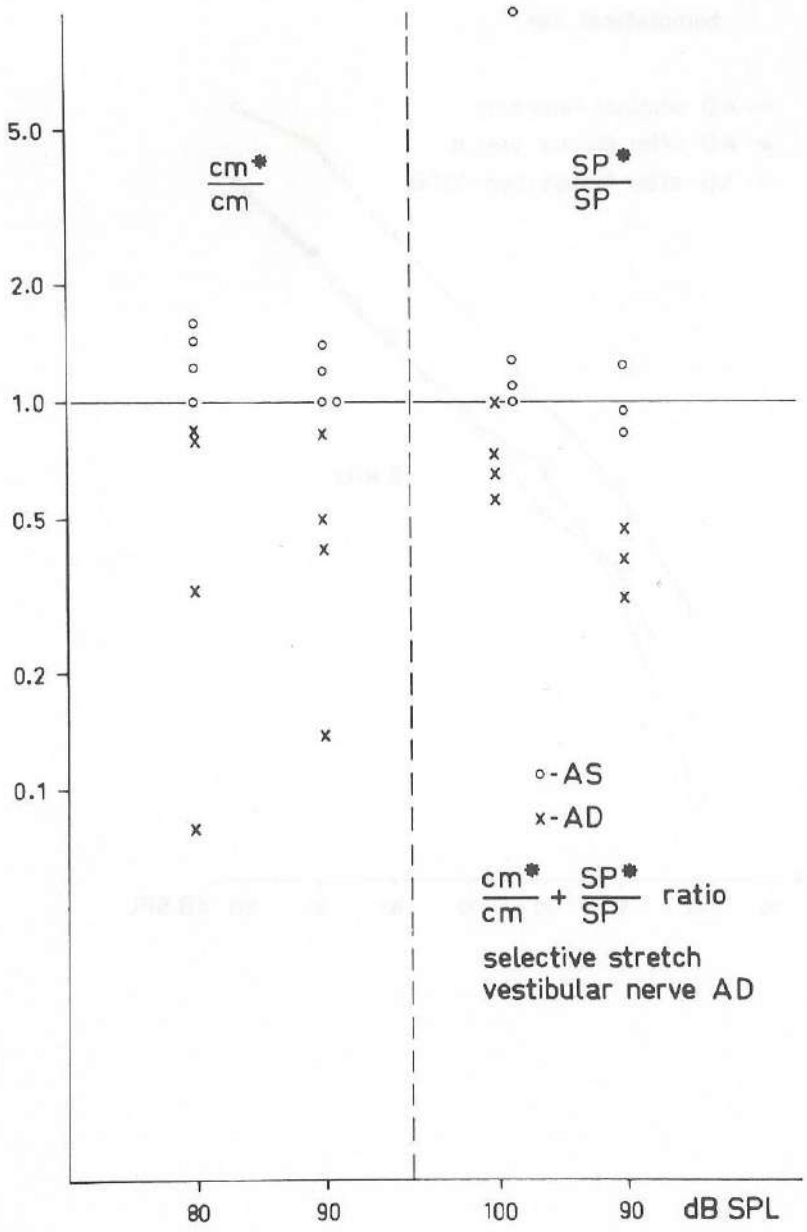


Fig. 32 The recording of the cochlear potentials shows the homolateral reduction of SP and CM after homolateral (AD) vestibular nerve stretch. The contralateral (AS) recorded CM-amplitude is increased. The contralateral SP-amplitude is not changed.

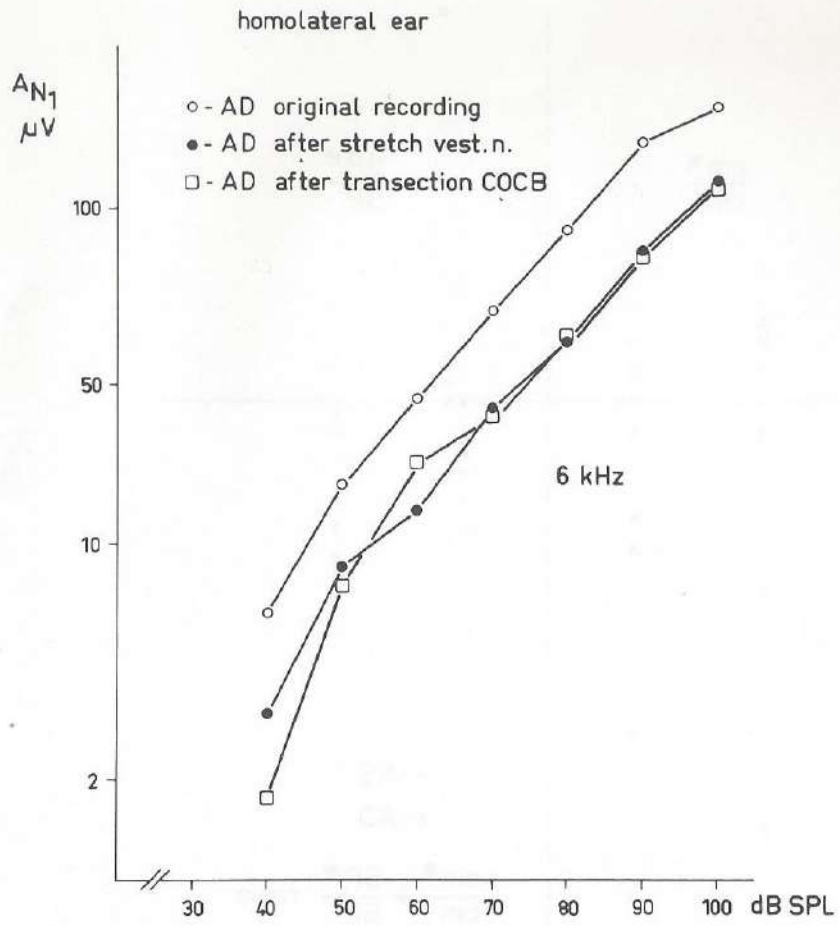


Fig. 33 The I/O-curve after selective stretch of the homolateral (AD) vestibular nerve shows an overal N_1-amplitude reduction, which is not influenced by COCB-transection.

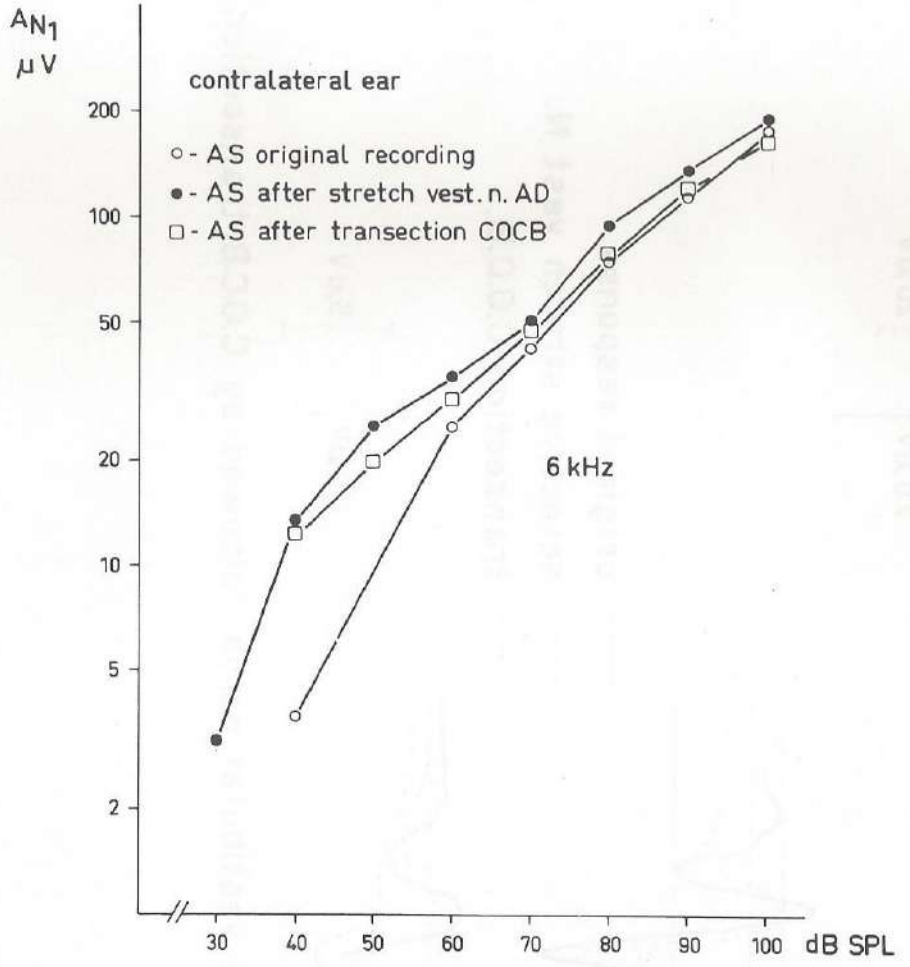


Fig. 34 The contralateral I/O-curve after selective stretch of the homolateral (AD) vestibular nerve shows an overall amplitude increase. COCB transection has only a minor effect on the N_1-amplitude.

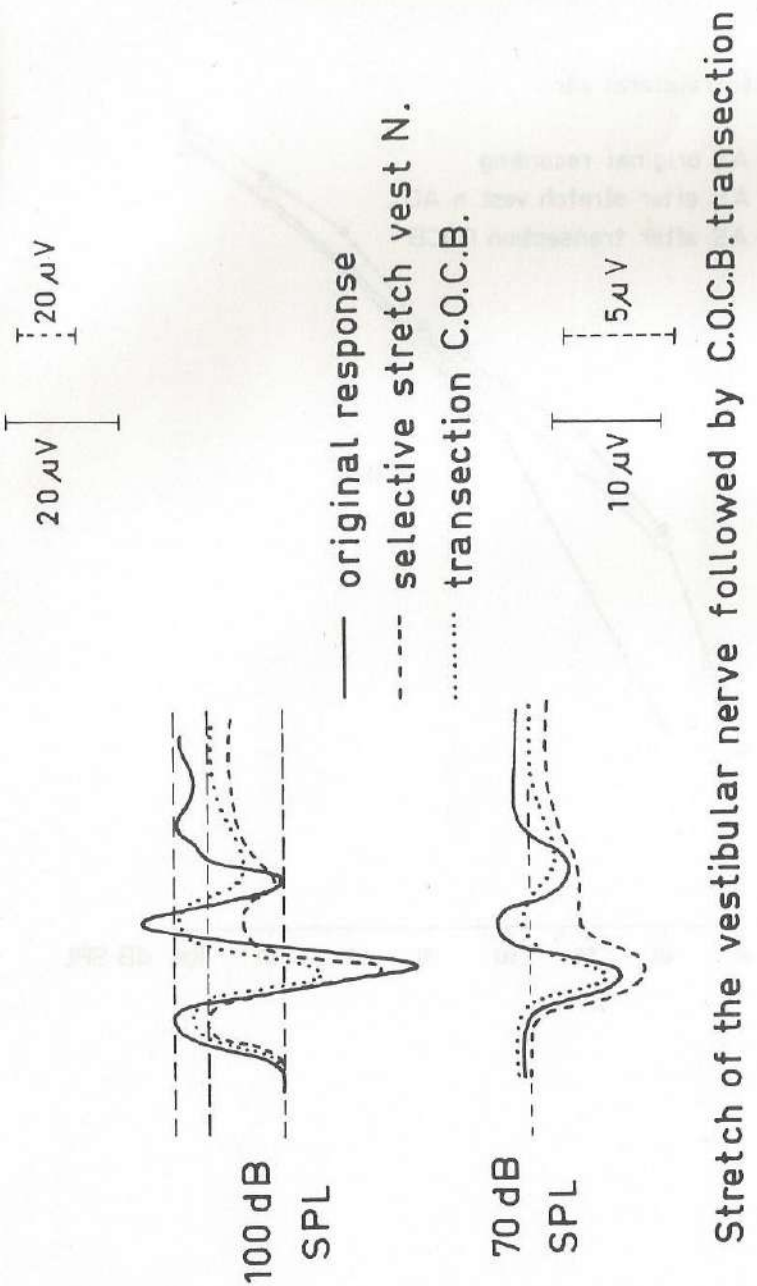


Fig. 35 This figure shows 2 experiments in which the vestibular nerve was stretched, (monophasic response), followed by COCB transection (diphasic response).

At 100 dB SPL the SP-amplitude is reduced after selective stretch of the vestibular nerve.

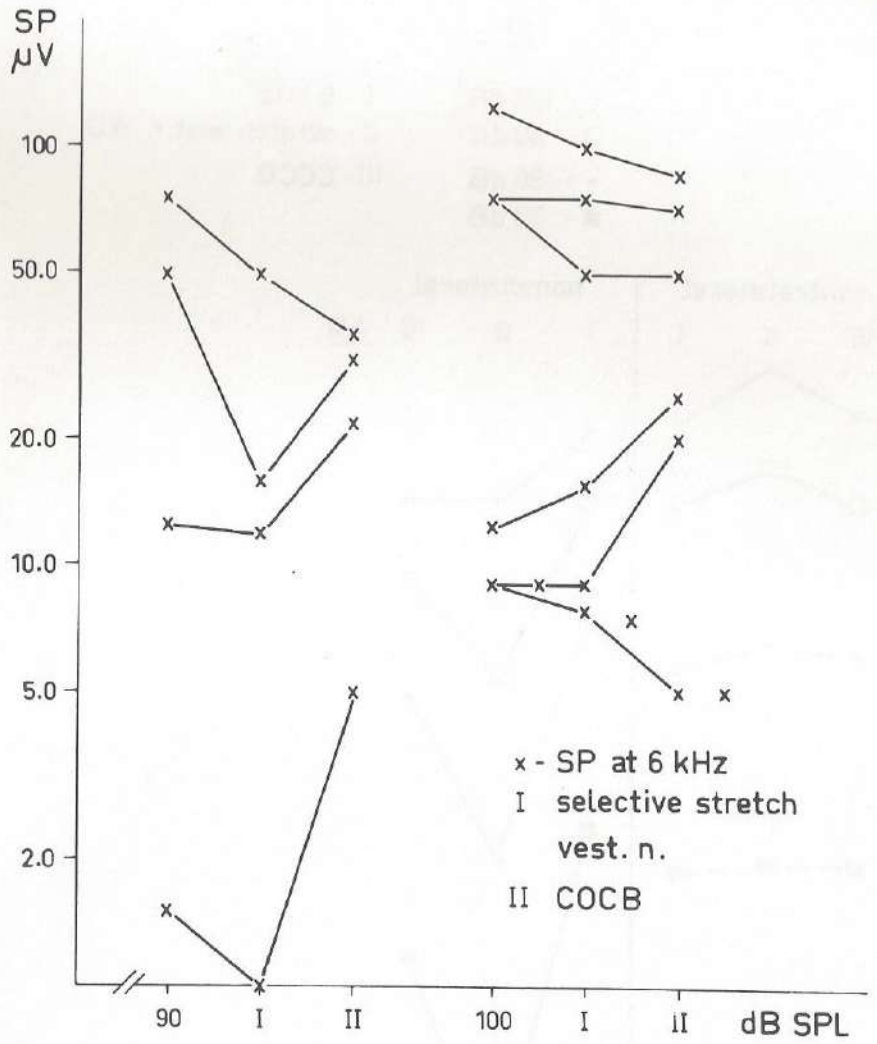


Fig. 36 The SP-amplitude is reduced after stretch of the vestibular nerve and shows a tendecy to restore to normal after COCB-transection.

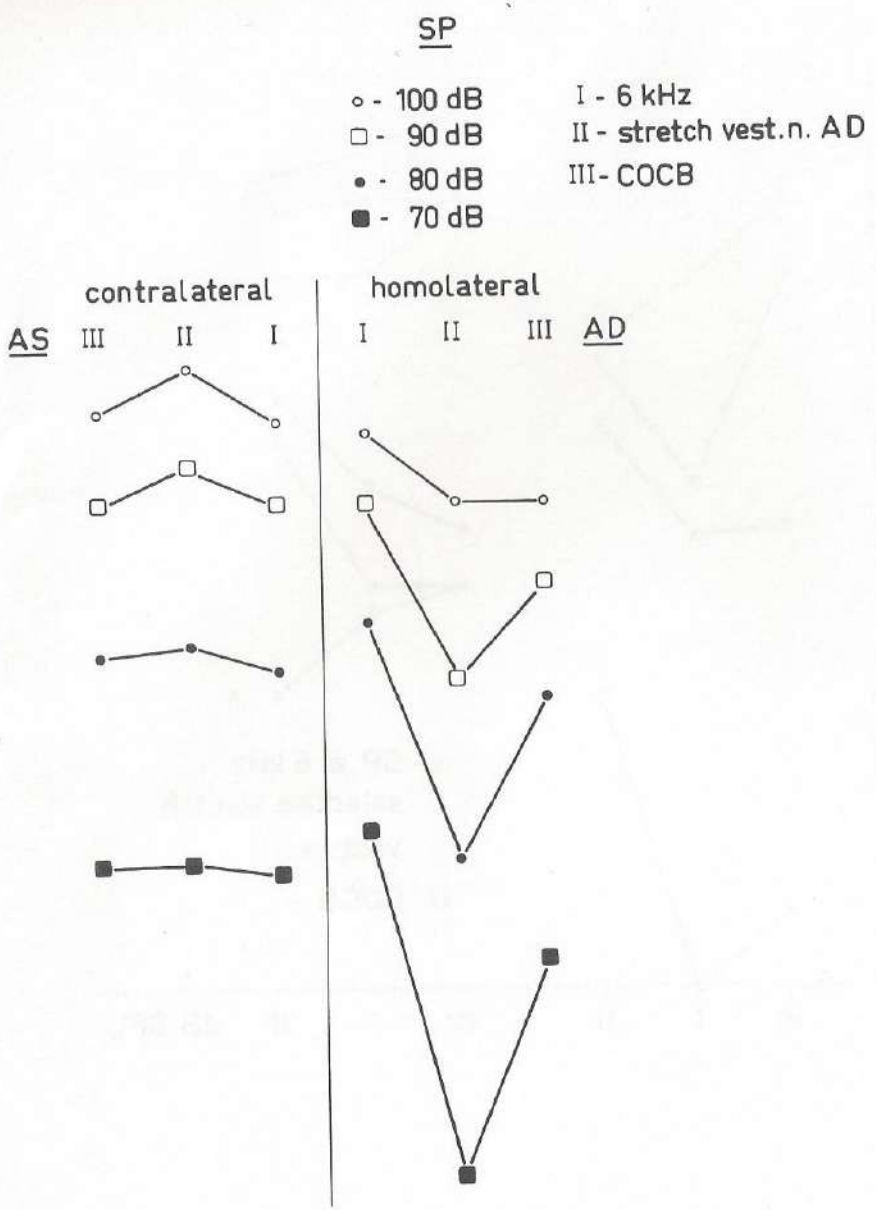


Fig. 37 In this illustration it is shown that the SP-amplitude on the homolateral (AD) side is reduced after vestibular nerve stretch, and, increased on the contralateral side (AS). After COCB transection the reduced homolateral SP increase, while the increased contralateral SP is restored to its initial values.

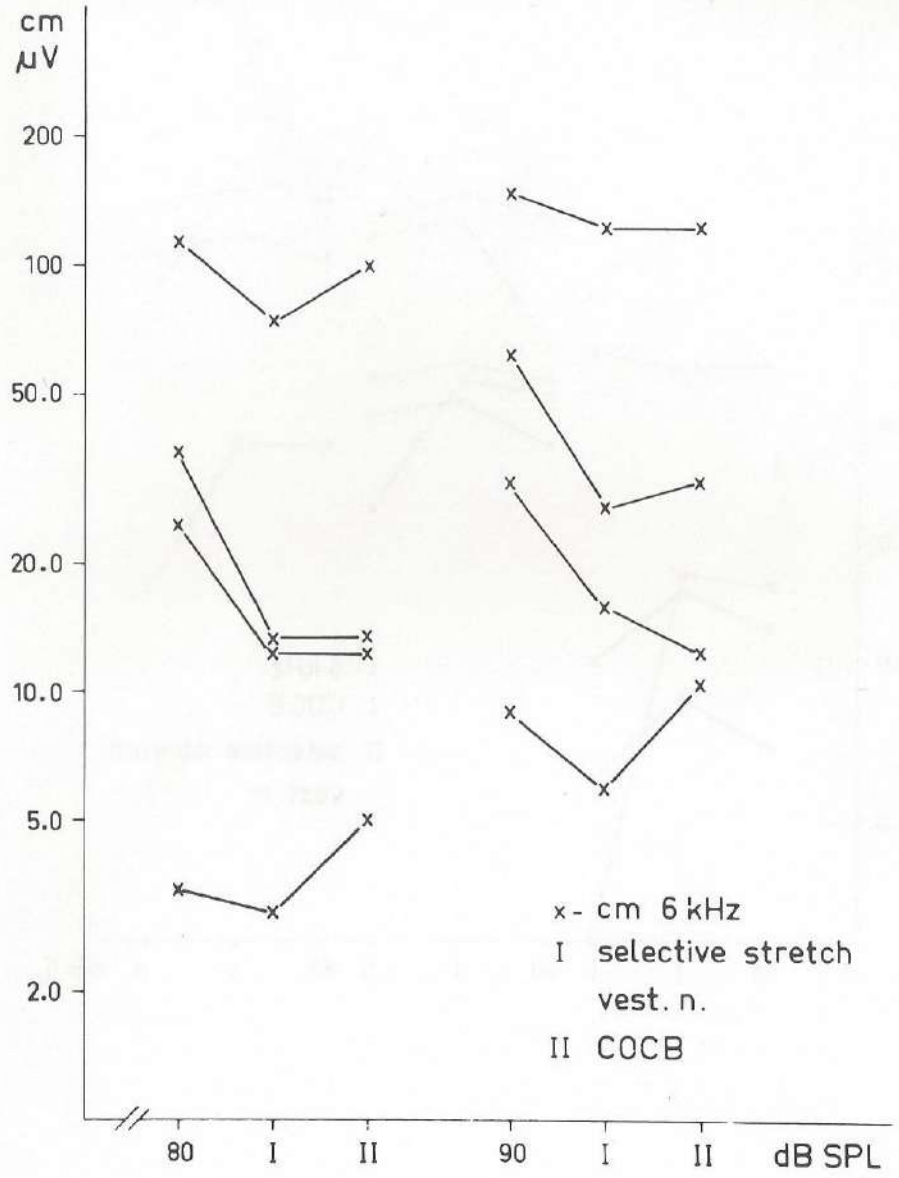


Fig. 38 This figure shows the CM-amplitude in 4 experiments after selective stretch of the vestibular nerve, followed by transection of the COCB. In most experiments the CM amplitude increases after COCB-transection.

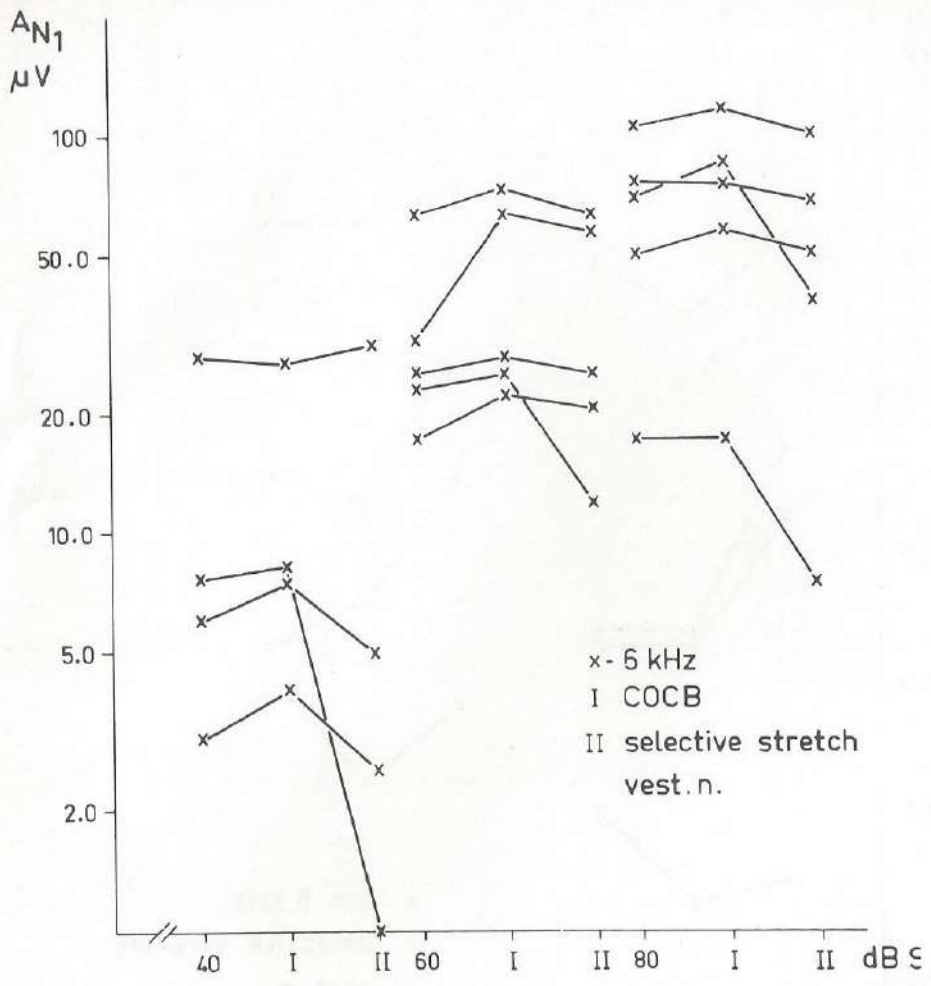


Fig. 39 In 4 experiments the N_1-amplitude is recorded after transection of the crossed olivocochlear bundle, which generally results in a slight amplitude increase. Subsequent stretch of the vestibular nerve results in a moderate reduction of the N_1-amplitude (See also fig. 33).

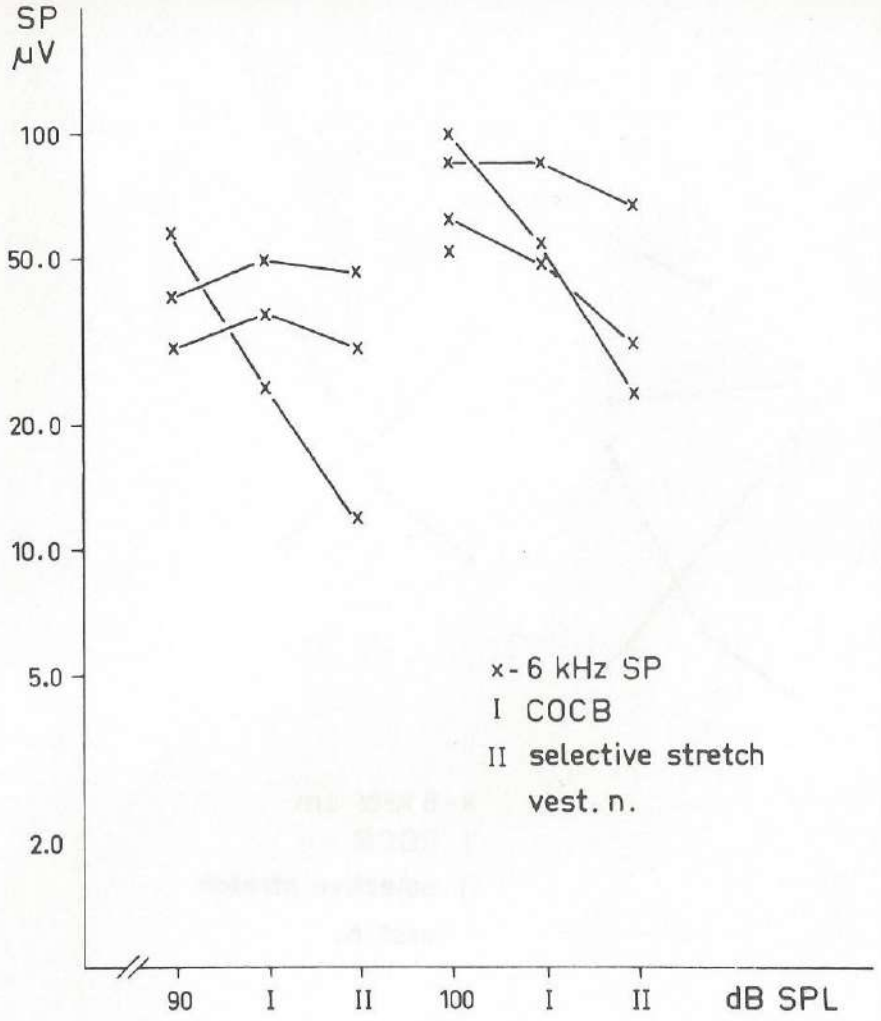


Fig. 40 This illustration shows the SP-amplitude after COCB-transection, followed by selective stretch of the vestibular nerve.

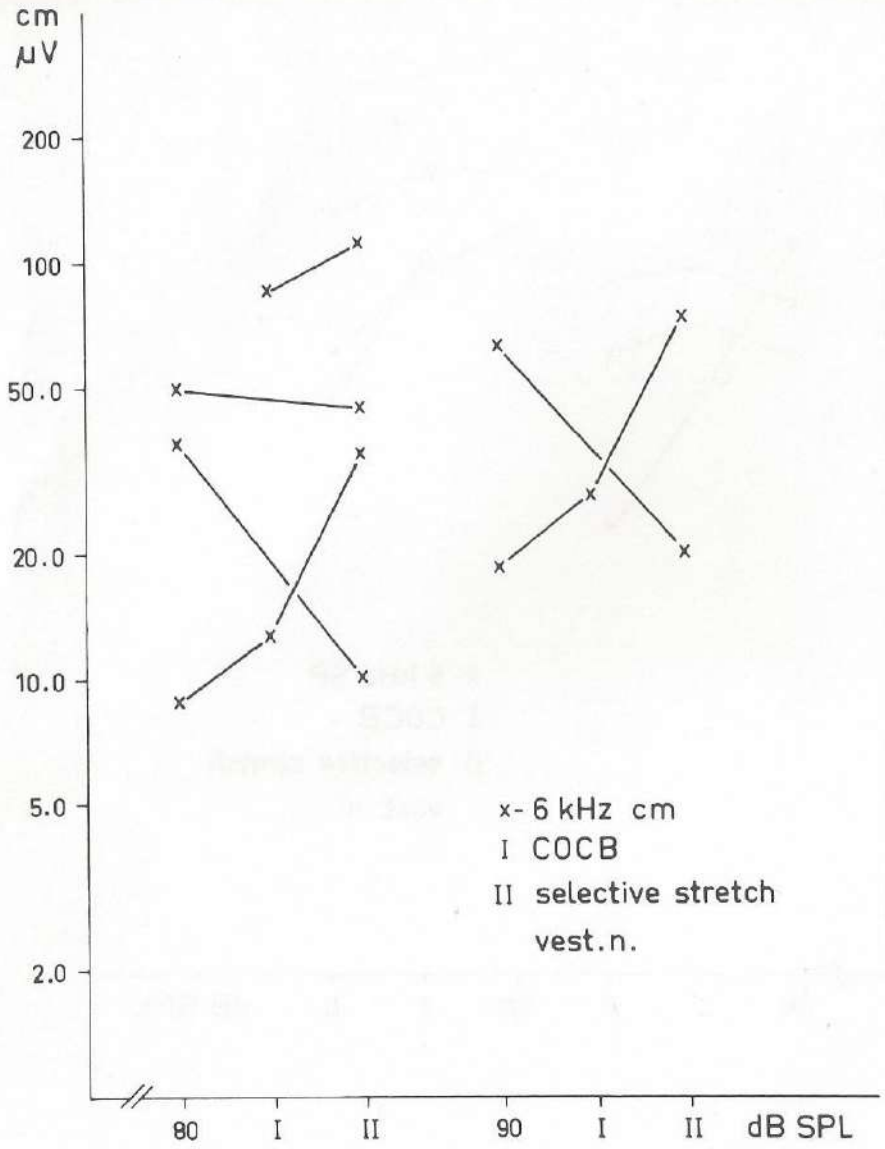


Fig. 41 The CM-amplitude is illustrated after COCB-transection followed by selective stretch of the vestibular nerve.

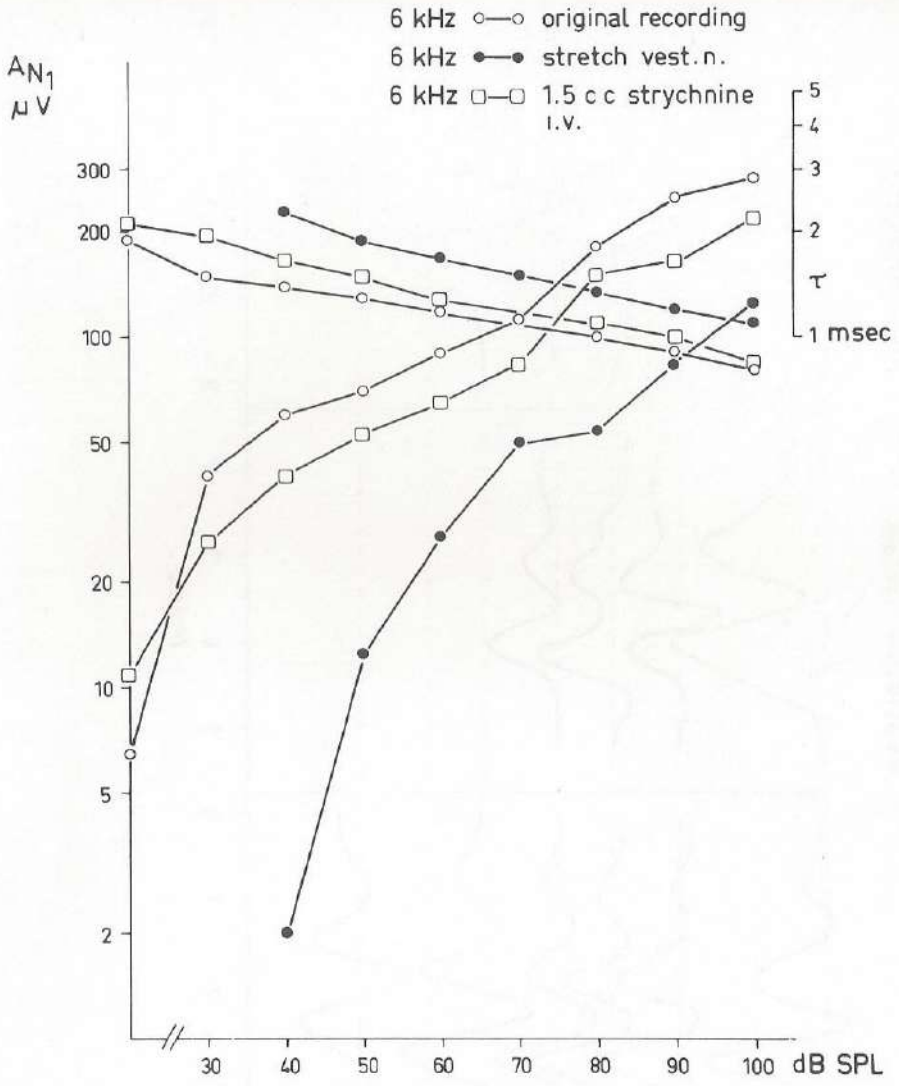


Fig. 42 The I/O-curve is shown at 6 kHz after selective stretch of the vestibular nerve, followed intravenously administrated strychnine-nitrate. A marked amplitude reduction occurs after stretch of the vestibular nerve which is partially restored after strychnine administration. This also holds for the N_1-latency.

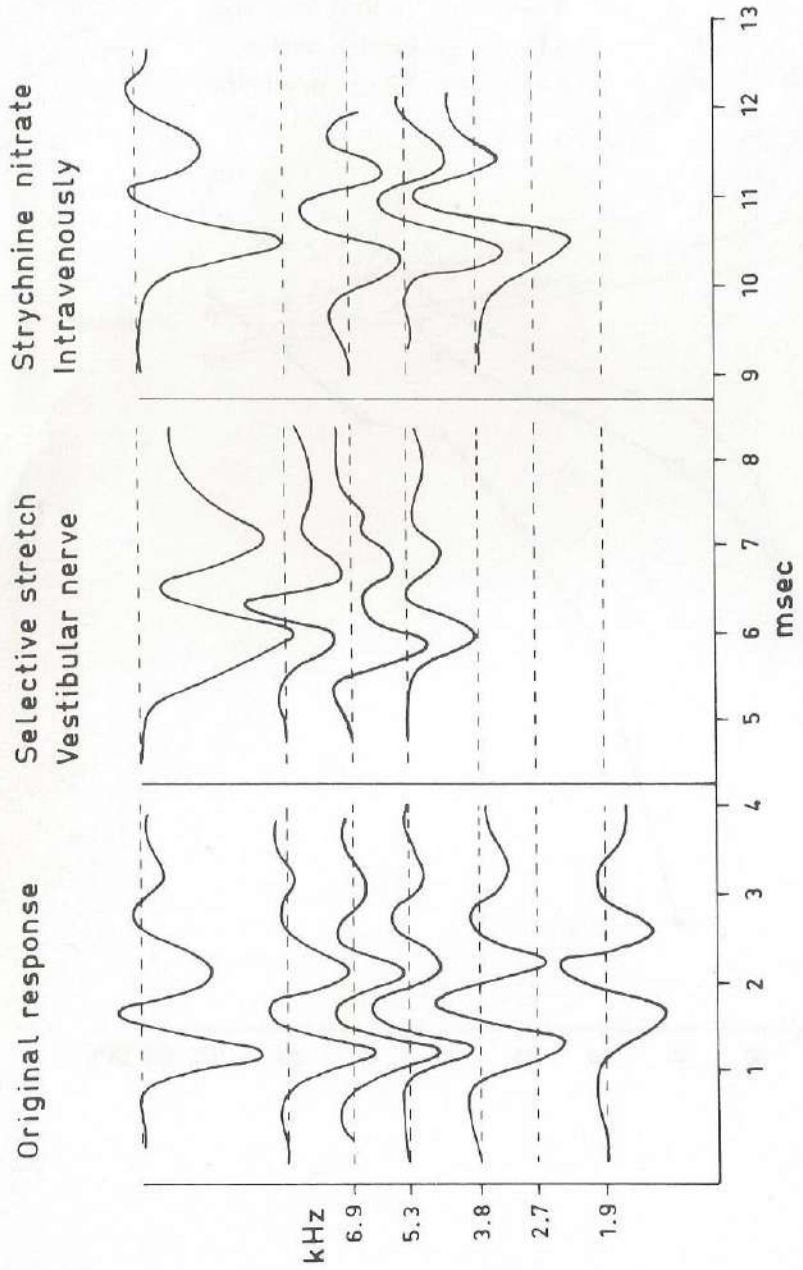


Fig. 43 The narrow-band responses are illustrated in this figure after stretch of the vestibular nerve followed by strychnine administration. At 6.9 kHz the monophasic response after vestibular nerve stretch is restored by the administration of strychnine.

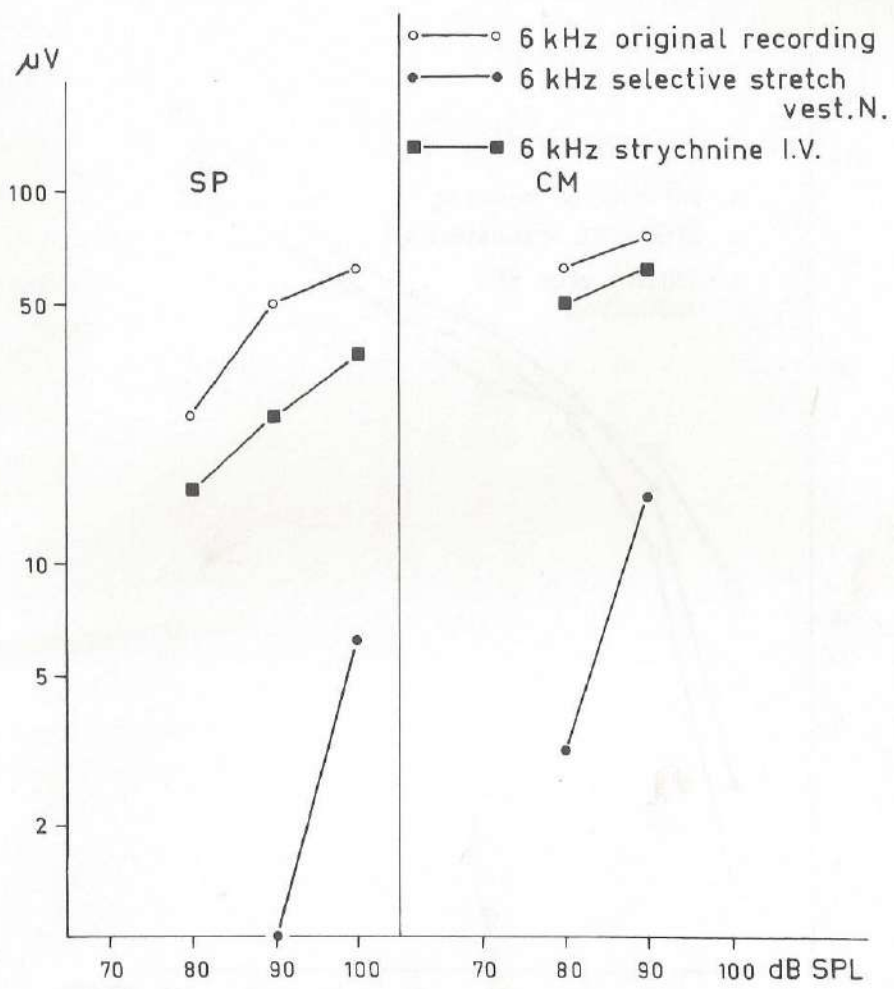


Fig. 44 This illustration shows the effect of vestibular nerve stretch followed by strychnine administration on the cochlear potentials CM and SP. The reduced amplitudes are almost restored to their initial values after strychnine administration.

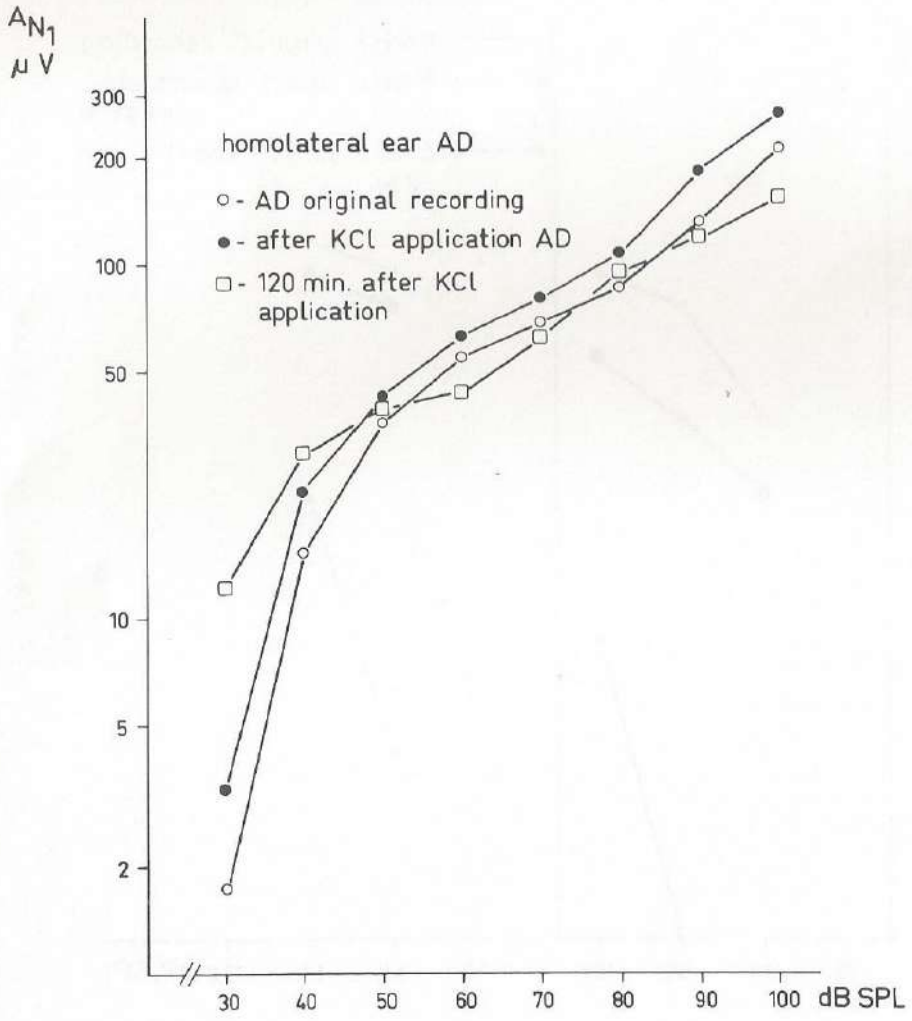


Fig. 45 The I/O-curve is shown after homolateral (AD) application of KCl on the vestibular nerve. This results in an overall N_1-amplitude increase. After 120 min. the N_1-amplitude is restored to normal (See also fig. 46).

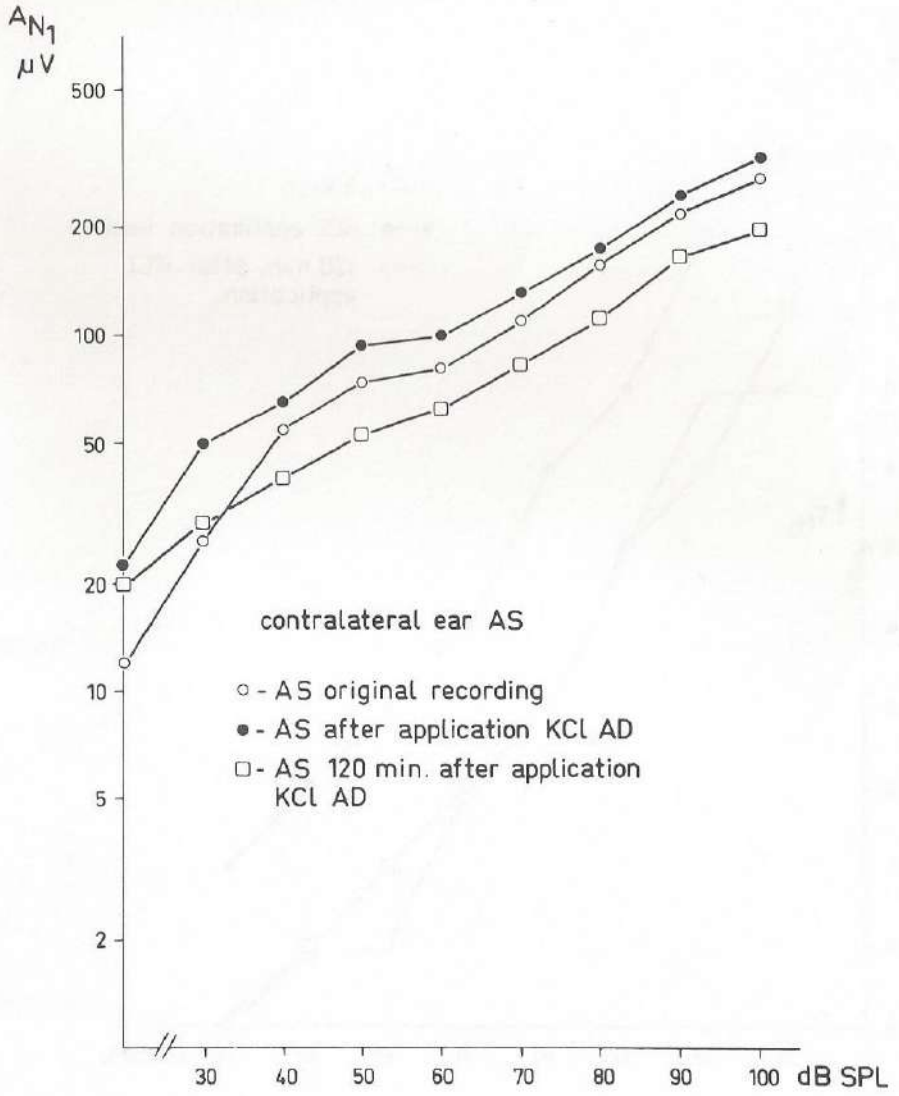


Fig. 46 The I/O-curve at the contralateral (AS) side after homolateral KCl application also shows an overall increase in N_1-amplitude.
Two hours later the N_1-amplitudes at all intensities have been reduced below their initial values.

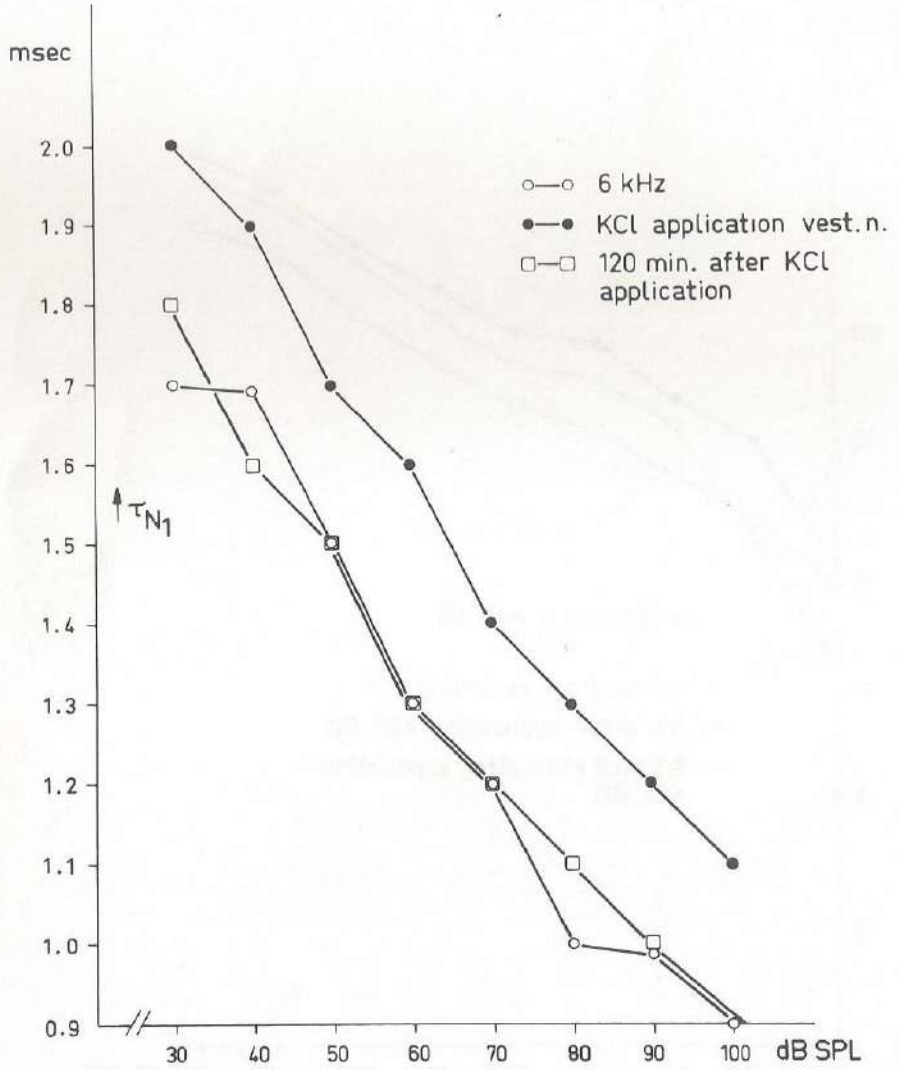


Fig. 47 The latency-intensity curve is shown after application of KCl on the vestibular nerve. This results in a marked latency (τ) increase. Two hours later in N_1-latency becomes normal again.

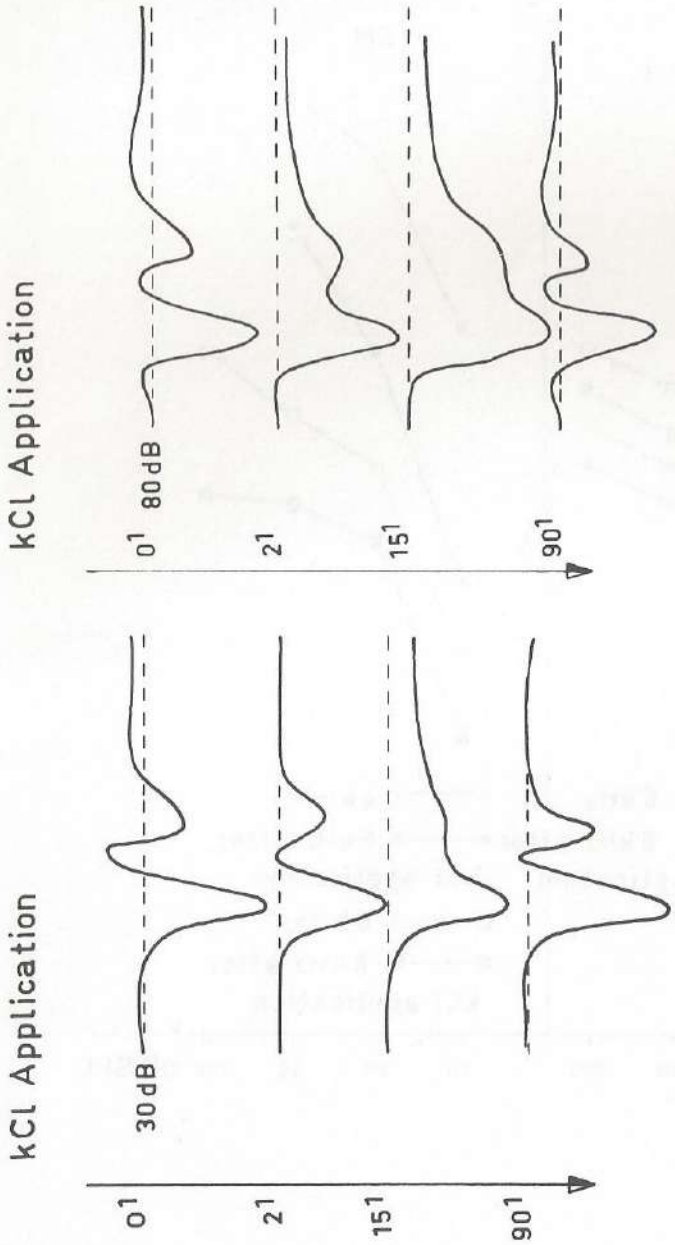


Fig. 48 The whole nerve response at 6 kHz is shown at 30 dB and 80 dB SPL after KCl application on the vestibular nerve. At 80 dB SPL the AP-waveform has become monophasic after 2 minutes while the AP-waveform at 30 dB SPL is still diphasic.

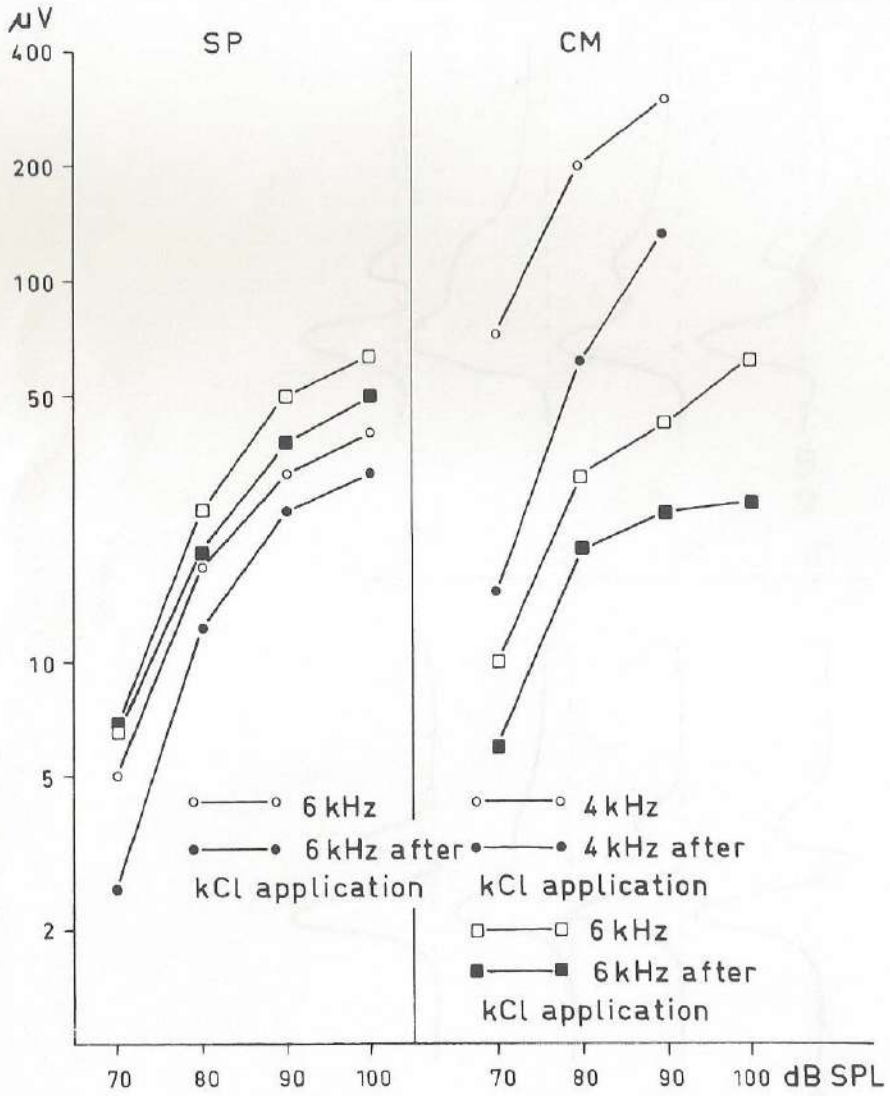


Fig. 49 This illustration shows the effect of KCl application on the amplitudes of the cochlear potentials CM and SP.
The application of KCl results in a marked reduction of CM and SP amplitudes.

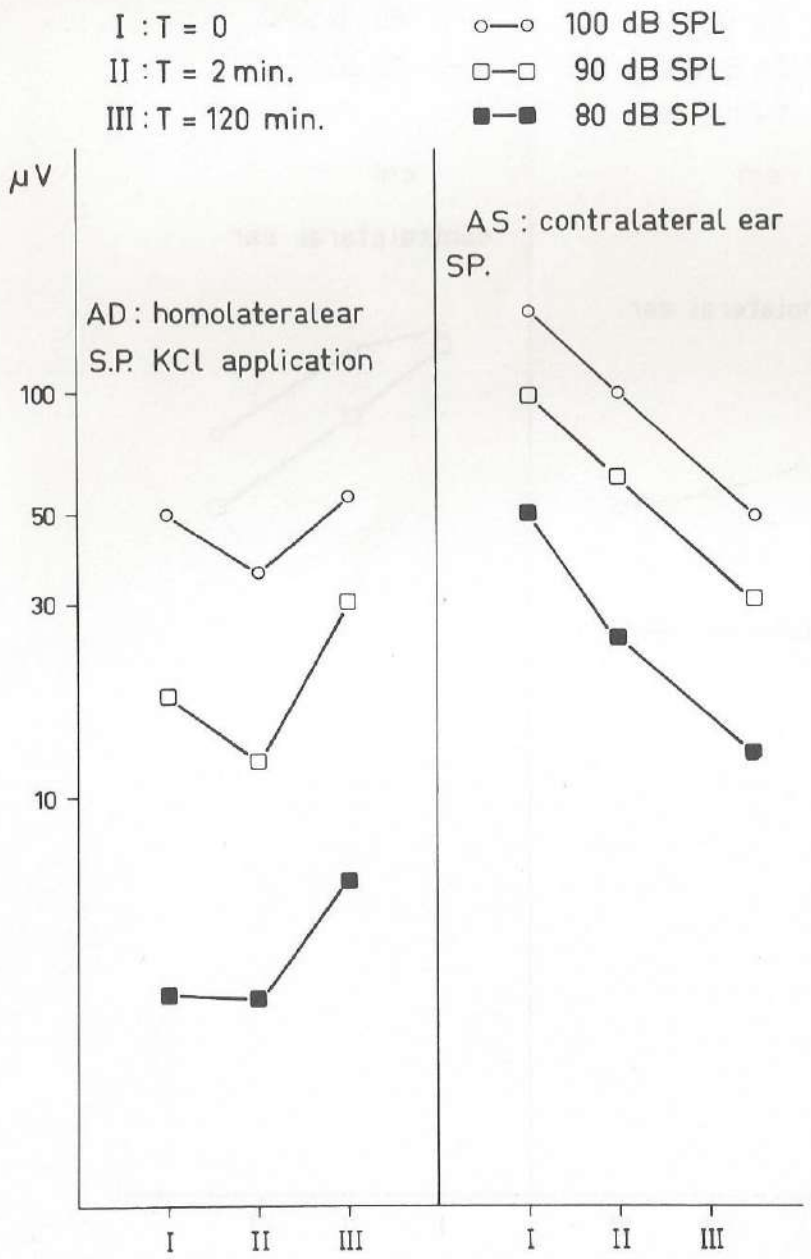


Fig. 50 In this figure the SP-amplitudes AD and AS are shown after homolateral (AD) KCl application.
After 120 minutes homolateral SP-amplitudes are restored towards their initial values, while the contralateral SP-amplitudes are still further reduced.

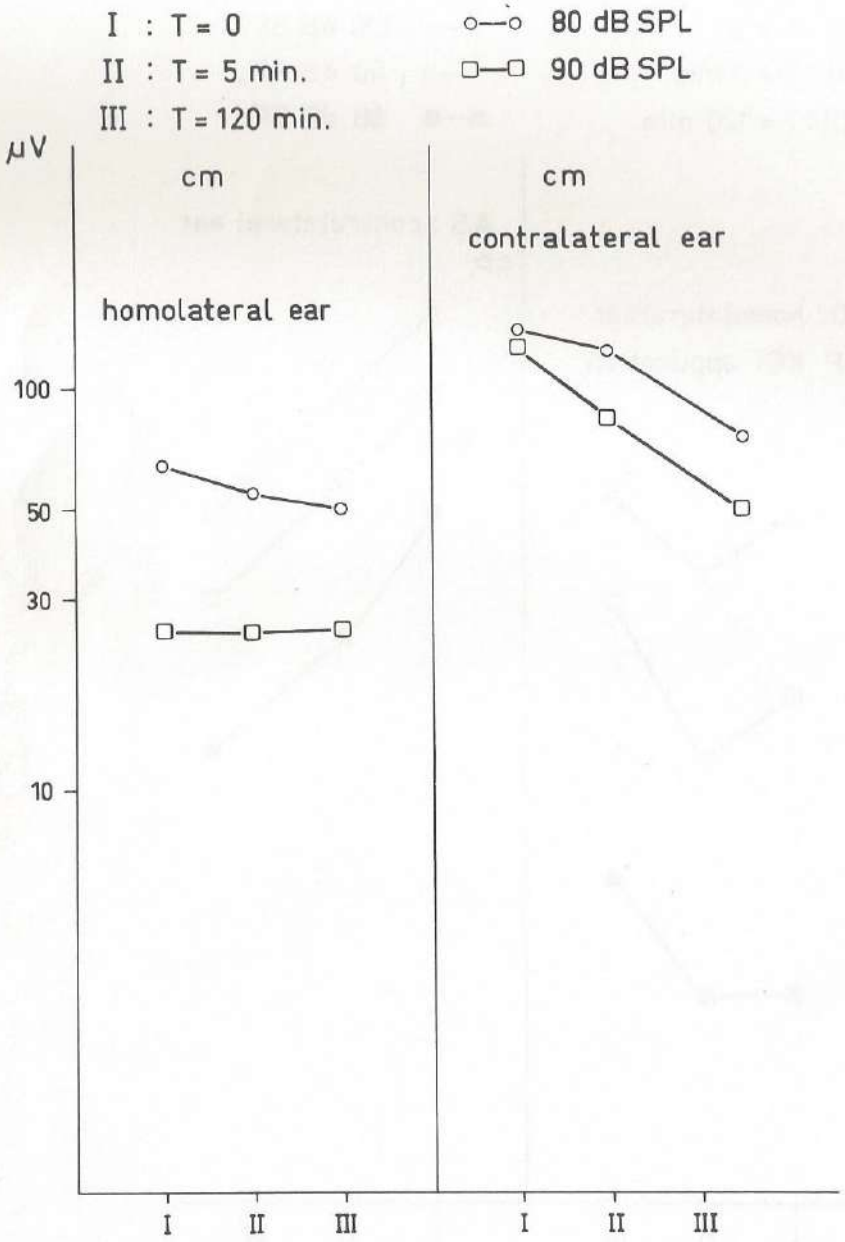


Fig. 51 In this illustration the CM-amplitude (AD + AS) are shown after homolateral (AD) KCl application. The contralateral (AS) CM-amplitudes are markedly reduced.

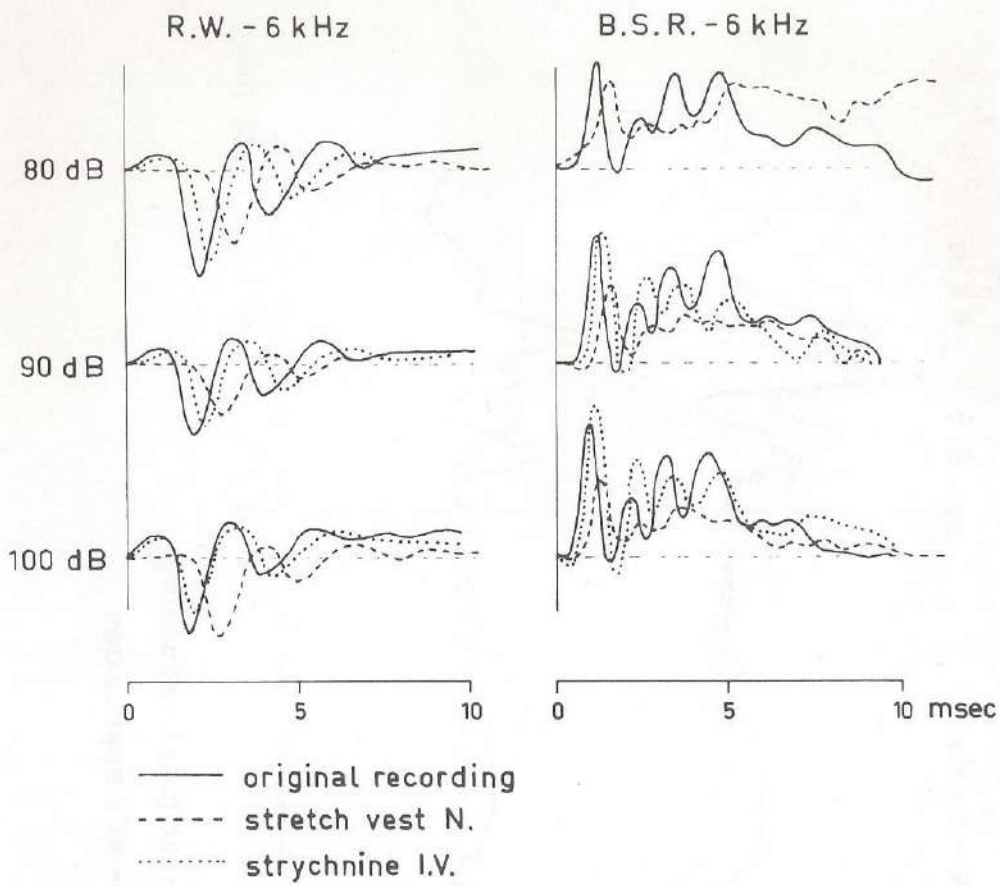


Fig. 52 In this illustration the round window (r.w.) and brainstemm responses (b.s.r.) are shown at 6 kHz after selective stretch of the vestibular nerve followed by strychnine administration. Note the N_1-latency increase and the loss of the positive peak after vestibular nerve stretch (r.w.). Peak II, III, IV and V are almost completely lost after vestibular nerve stretch (b.s.r.). Strychnine does restore the r.w. and b.s.r. towards the original waveform.

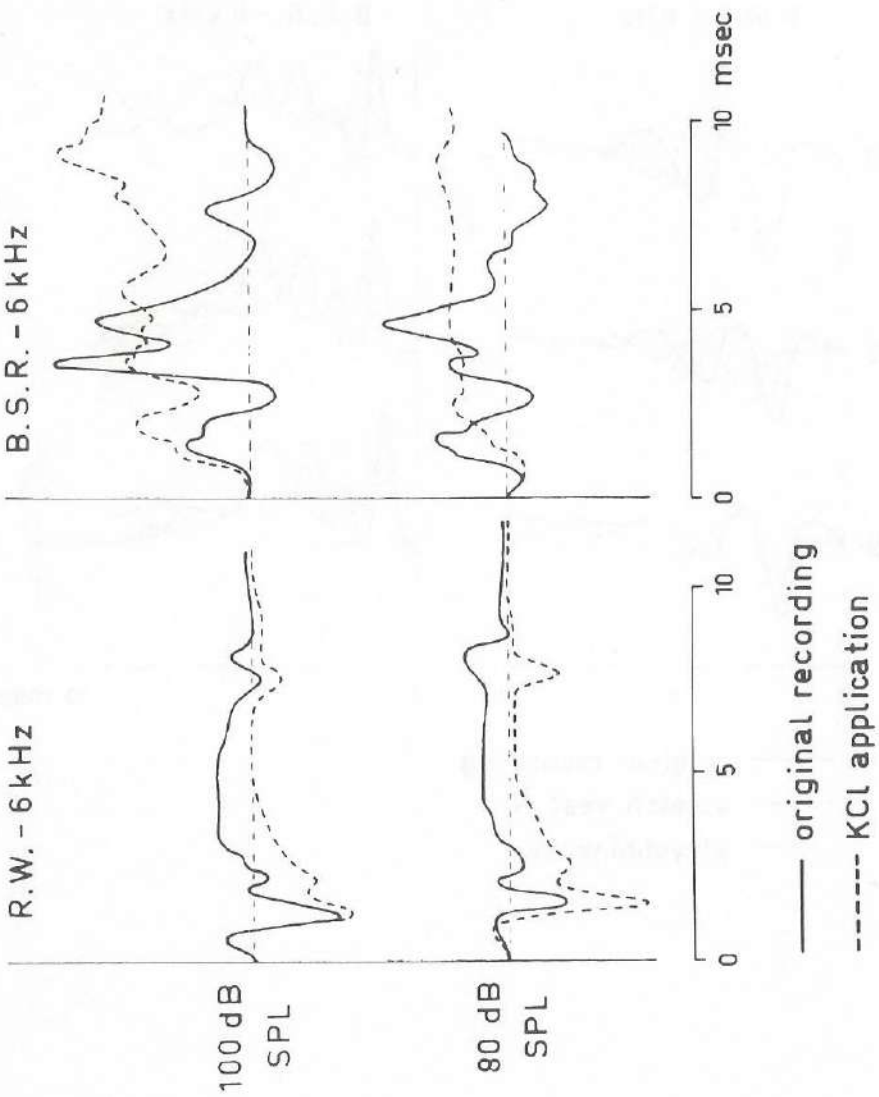


Fig. 53 In this illustration the round window (r.w) and brainstem responses (b.s.r.) are shown after application of KCl on the vestibular nerve. KCl does not block the afferent input, but the characteristic peak in the brainstem recording are lost.

The endolympahtic potential is + 80mVolt, mediated by the vascular stria, and is supposed to be constant.
When the efferent nerve system is activated the resistance Re will be reduced and current is shunted away from the inner hair cells resultant in a reduced AP-amplitude.

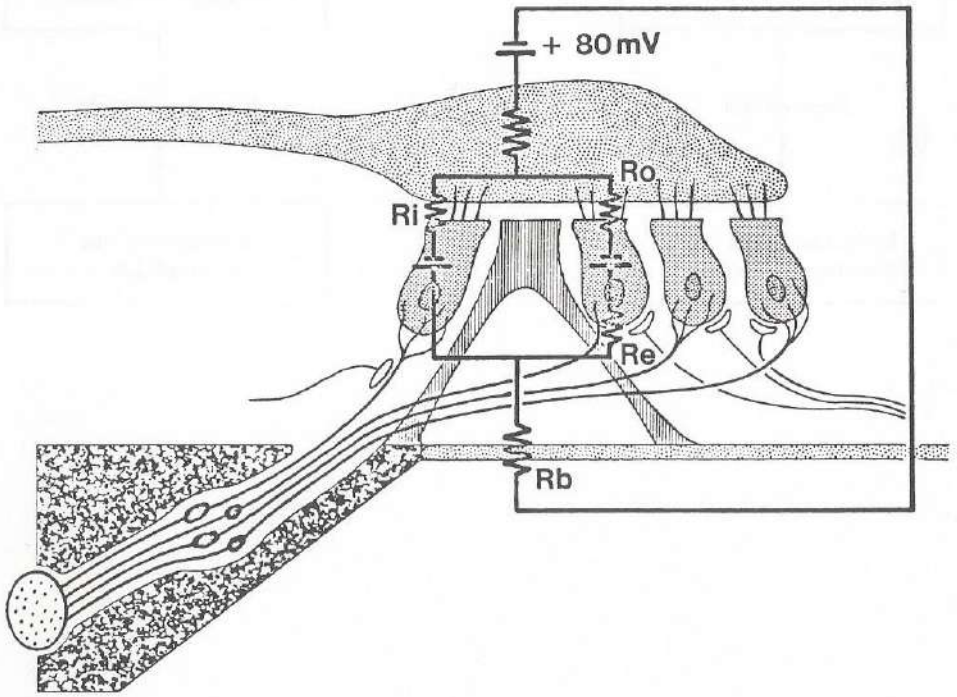


Fig. 54 Electrical model of cochlear afferent and efferent innervation (Adjusted to Wiederhold and Geisler).

Ri = resistance in the inner hair cell circuit
Ro = resistance in the outer hair cell circuit
Re = resistance in the outer hair cell circuit influence by efferent nerve activity
Rb = resistance of the basilar membrane.

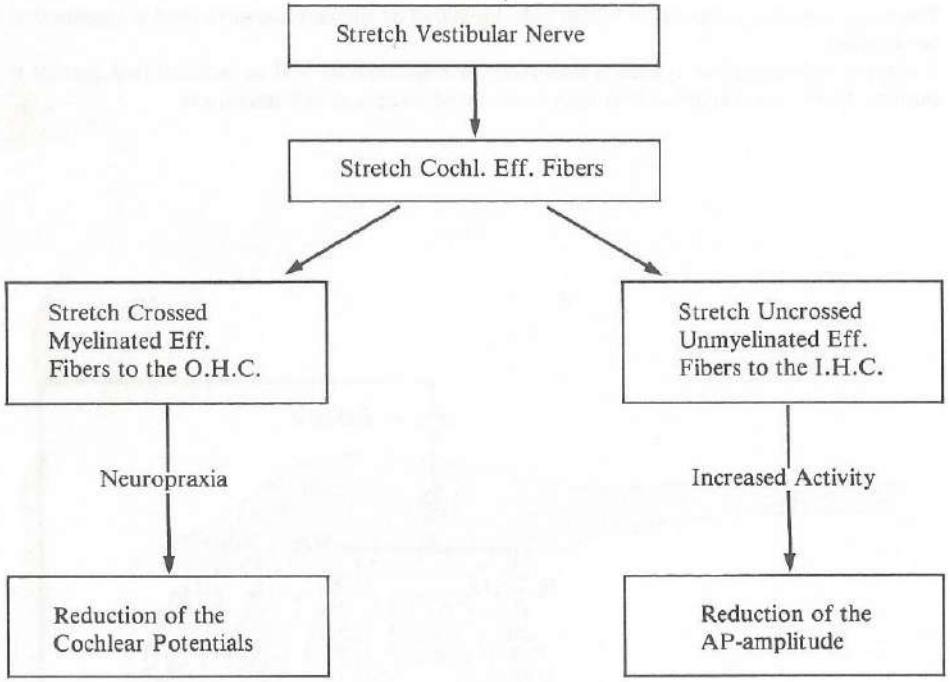


Fig. 55 The effects of selective vestibular nerve stretch are demonstrated in this illustration. The reduction of the CM and SP amplitude as well as the AP-amplitude is based on the assumptions that

1) myelinated efferent nerve can be blocked by the neuropraxia phenomena
2) unmyelinated efferent nerve activity is increased after stretch, pressure
3) crossed efferent nerve fibers innervate O.H.C., uncrossed mainly I.H.C.
4) myelinated nerve end upon O.H.C., umyelinated on I.H.C.

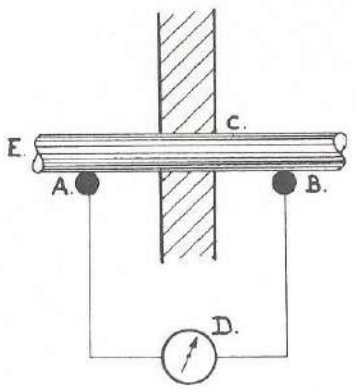
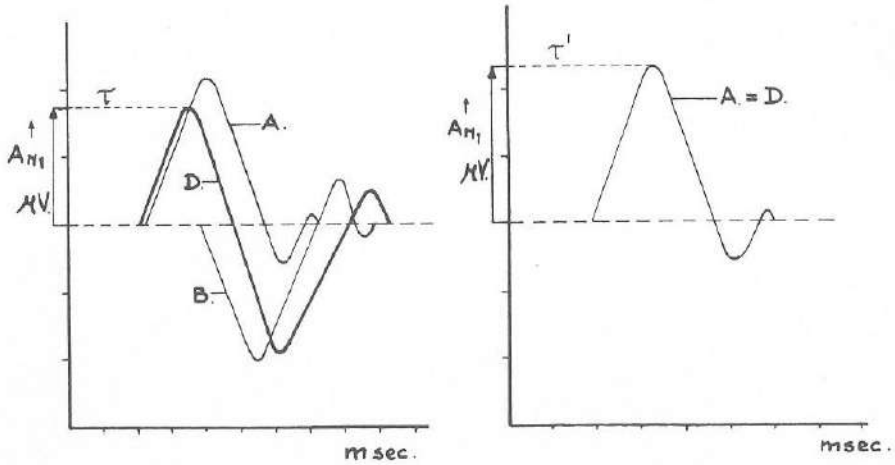


Fig. 56



A = response recorded by electrode A
B = response recorded by electrode B
D = resultant response recorded at r.w.
τ = N_1-latency
A_{N_1} = N_1-amplitude

Situation after complete nerve conduction block. No recording by electrode B. The resultant response D is similar to the response recorded by electrode A.
$\tau' < \tau$ $A'_{N_1} < A_{N_1}$

(a) S-shaped olivary segment
(b) Accessory olive
(c) Trapezoidal body nucleus
(d) Cochlear nerve
(e) Vestibular nerve
(f) Genu facial nerve

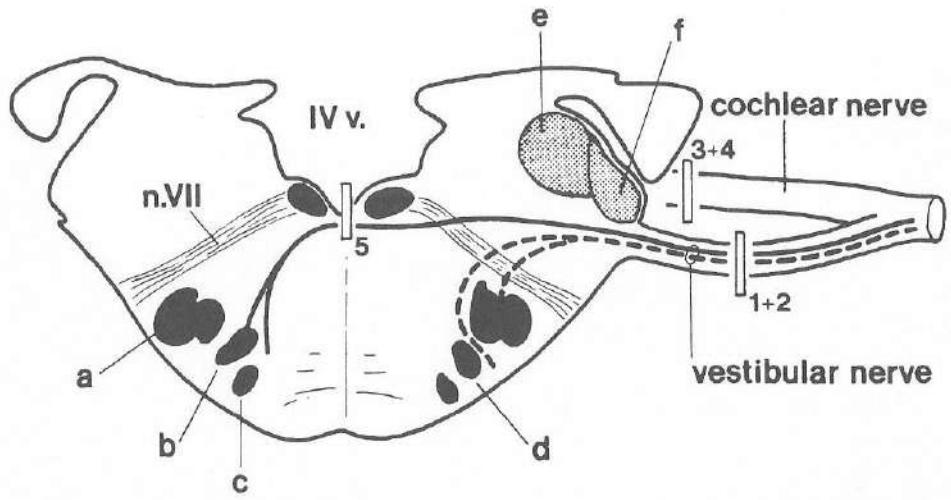


Fig. 57 Schematic drawing illustrating the origin of the efferent cochlear fibres. The lesions in the various experiments are shown in this figure

1 + 2 Selective stretch/transection vestibular nerve
3 + 4 Selective stretch/transection cochlear nerve
5 Transection of the crossed olivo cochlear bundle
_____ crossed olivo cochlear bundle
---------- uncrossed olivo cochlear bundle