Ann. Rev. Pharmacol. Toxicol. 1982. 22:383–412

NEUROTRANSMISSION IN THE AUDITORY SYSTEM: A PRIMER FOR PHARMACOLOGISTS[1]

Paul S. Guth and Brian Melamed

Department of Pharmacology, Tulane University School of Medicine
and Kresge Hearing Research Laboratory of the Louisiana State University
Medical Center, New Orleans, Louisiana 70112

Sensory processes have not been a traditional concern of pharmacologists. An occasional review article on the pharmacology of sensation has appeared but the pharmacological literature concerned with afferent or sensory systems is practically nonexistent. This, despite the fact that the information transfer in afferent or sensory systems apparently involves that favorite playground of the neuropharmacologist, the chemically-mediated synapse, as much as efferent systems do. There is an inertia in pharmacological thought which tends to produce continued interest and productivity in efferent and central systems but opposes efforts to move into nontraditional areas such as sensation. Pharmacologists, furthermore, are not trained to deal with sensory processes and so sensation has been out of the pharmacological mainstream. One result of this neglect is the fact that with the still arguable exceptions of substance P and adenosine triphosphate none of the primary afferent transmitters has been identified. In fact, as will be clear later, some of the primary afferent transmitters may not belong to the universe of classical putative transmitters at all.

Pharmacologists commonly say that drugs affecting nervous structures do so mainly by influencing processes associated with transmission. That is, that chemical transmission, as against conduction, is a particularly drug-

[1]This article was written while the authors were supported by grants 5P50-NS-11647 (P. Guth) and NS-07058 (B. Melamed) from the National Institutes of Health.

0362-1642/82/0415-0383$02.00

sensitive process. It is not clear whether this generalization is really true or that pharmacologists, like the blind men and the elephant, describe as sites of action only those which they happen to be observing at the moment. Since chemical transmission has held the center of the neuropharmacological stage, that process becomes the major focus of attention of this article. (Electrotonic transmission has not yet been described along the auditory pathway.) It is our guess that the development of a rational therapeutics of sensory systems will depend on the understanding of the nature of sensory transmission. Thus, we present this review article as prelude to the development of such therapeutics and to nudge sensation a bit further into pharmacological consciousness.

Major research attention has been focused on transmission at the synapses of the cochlea and cochlear nucleus. The higher auditory pathway has received much less attention in this regard. The organization of this article will reflect those emphases.

The limited space available for this review precludes the presentation of detailed information on the anatomy of the cochlea and higher auditory structures, their blood supplies, and methods applicable to the study of the pharmacology of these structures. These subjects have been reviewed elsewhere. A previous review article (1) contains synopses of cochlear blood supplies and methods of interest to pharmacologists as well as citations of other reviews dealing with blood supply, anatomy, and methods.

AFFERENT TRANSMISSION IN THE COCHLEA

Hallowell Davis called the cochlea "a roomful of treasures" and the interested neuropharmacologist-synaptologist will find it so. Not only does it have several different synapses but the chambers or scalae of the cochlea (Figure 1) can be perfused and the perfusate collected. This arrangement permits close drug applications bypassing the blood-cochlear barrier (2) as well as collection of substances (e.g. transmitters) elaborated by cochlear structures (3).

The afferent synaptological treasures are those found between the two varieties of sensory cells called inner and outer hair cells (Figure 1), and the afferent dendrites of the VIII nerve. There are also reciprocal synapses and dendro-dendritic synapses associated with the afferent fibers. The efferent innervation of the cochlea consists of the olivo-cochlear bundle (both ipsi- and contralateral) and the autonomic (sympathetic). There was a suggestion that a reticulo-cochlear innervation existed (4) but this has not been confirmed.

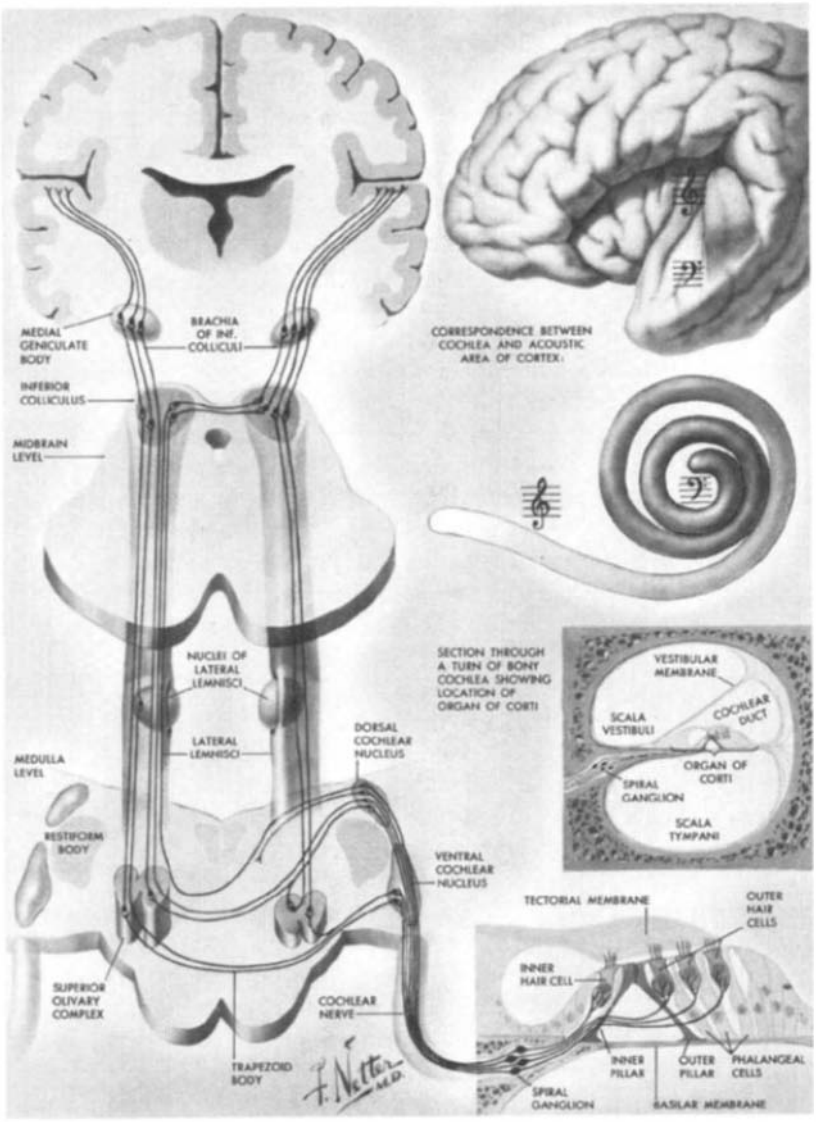

Figure 1 This figure is grossly oversimplified but may be useful for the uninitiated. Not shown, for example, are the centrifugal innervations of the cochlea and the cochlear nuclei.

Ultrastructure of the Afferent Synapse

The structural characteristics of the hair cell-VIII nerve synapse are similar to those of other chemically-mediated synapses. Although the specific features vary from species to species, there is typically a synaptic cleft of 20 nm width filled with filamentous material. The postsynaptic membrane is generally thickened and electron-dense. Presynaptically, the hair cell exhibits specializations in the form of localized membrane thickenings and an electron-dense body, rod-shaped or spherical, called a synaptic body, which is 0.1 to 0.4 μm in height or diameter, and which is surrounded by a relatively small number of electron-transparent vesicles of 30 to 50 nm diameter. There is no morphological evidence of electrotonic junctions between the hair cell and the VIII nerve fibers.

Smith & Sjostrand (5, 6) first described the ultrastructural features of the afferent synapse in inner and outer hair cells of the guinea pig cochlea. Presynaptically, the synapse is characterized by the presence of a relatively large osmiophilic mass, rod-like in shape, called a synaptic body, surrounded by a single layer of synaptic vesicles. The inner hair cells exhibit a narrow, localized thickening beneath the synaptic body and an indentation of the postsynaptic membrane. These characteristics are not obvious at the outer hair cell synapse.

Similar synaptic features have been described in the cochlea of the newborn mouse (7), the monkey (8), the rabbit (9), and man (10). However, in the outer hair cells of the cat (10–12), the synaptic body is not visible and synaptic vesicles are not obvious. Freeze-fracture studies of the chinchilla cochlea have further elucidated the anatomical characteristics of the afferent synapse (13). While the synaptic structure, as revealed by freeze fracture, in the inner and outer hair cells resembles those of chemically-transmitting synapses, the authors suggest that the difference in structure between the inner and outer hair cells may mean that the two populations of hair cells may release different transmitters or have different transmitter mechanisms. Such a suggestion is also put forth by Dunn & Morest (10), who observed a difference in synaptic anatomy at the inner and outer hair cells of the cat cochlea.

In the mammal, the presence of the synaptic body is not a consistent feature of the hair cell-receptoneural junction. As Smith & Sjöstrand (5, 6) have pointed out, at some hair cell-VIII nerve synapses the synaptic body is not visible. In the cat and the chinchilla, the synaptic body is not evident at all in the outer hair cells.

The presence of a synaptic body is not unique to the hair cells of the acousticolateralis organs. Similar structures, termed synaptic ribbons or lamellae, have been demonstrated at other sensory synapses such as the

retinal rod cells (14), the photoreceptive cells of the pineal gland (15), and vertebrate taste buds (16). The function of the synaptic body is, at present, unknown, but several hypotheses concerning its function have been proposed. Osborne & Thornhill (17) suggest that the synaptic body, in connection with the synaptic rodlets, served to store the afferent transmitter, which is formed in the synaptic vesicles. An alternate proposal is that the synaptic body functions to localize the release of transmitter from synaptic vesicles (18, 19) and to regulate the release of transmitter from the vesicles (18, 19). While there is little direct anatomical evidence to suggest that the vesicle contents are released by exocytosis (such as the demonstration of omega figures), coated vesicles, presumed to be a remnant of the vesicular membrane, have been demonstrated in the hair cells of the pigeon basilar papilla (20) and in the goldfish saccular macula (21). On the other hand, Osborne & Thornhill (17) suggest that the afferent transmitter is released from the synaptic rodlets, where it may be stored, into the synaptic cleft by a gating mechanism rather than by exocytosis.

The anatomical evidence supports the hypothesis that transmission at the afferent synapse is chemically-mediated. The hypothesis is supported by evidence that there are not gap junctions between the hair cells and the afferent nerve fibers in the cat (10), the guinea pig (22), and the chinchilla (23, 24). But the paucity of vesicles at the receptoneural junction [Yamanda (25) has calculated that there are 200 to 300 synaptic vesicles to a synaptic body] suggests that, if the hair cells release transmitters from vesicles, the stimulation of the post-synaptic receptors by transmitter molecules must be extremely effective. Perhaps the receptors are exquisitely sensitive to the transmitter (i.e. the affinity of the receptor for the transmitter is very high), or the mechanisms for termination of action of the transmitter are not very effective. The suggestion has been made that the inner and outer hair cells of the cat and chinchilla may release different transmitters, based upon their differential ultrastructural anatomy (10, 113). Although this is indeed a possibility, one must consider Smith & Sjöstrand's (5, 6) findings that at some of the afferent synapses in the guinea pig, the synaptic body was not evident. The implication of such a differential transmitter hypothesis would be that, at least in the guinea pig, different outer hair cells in the same cochlea and perhaps different synapses in the same hair cell release different transmitters. A more conservative explanation may be that there are different mechanisms for transmitter release at these differing synapses, as has been proposed by Dunn & Morest (10) and Gulley & Reese (13). Nadol (25a) has reported on the presence of reciprocal synapses between outer hair cells and afferent endings in the organ of Corti of man.

Yet another possible site of afferent transmission in the cochlea bears mentioning. In the course of research efforts to discover evidence of synap-

tic coupling between the outer and inner hair cell systems, Bodian (26) found clefts between pairs of presynaptic efferent fibers. These clefts suggest the possibility of dendro-dendritic interaction. Such dendro-dendritic contacts seem, however, confined to the outer hair cell system. As with the reciprocal synapses at the bases of the hair cells the function of this contact site can only be wondered at.

Physiology of the Afferent Synapse

Principally because of the technical difficulties of obtaining intracellular recordings from VIII nerve dendrites in the cochlea, direct electrophysiological evidence that transmission at the hair cell-receptoneural junction is chemically-mediated has come from studies in lower vertebrates. A series of experiments by Furukawa et al (27) on the VIII nerve of the goldfish have characterized the postsynaptic responses during transmission at the hair cell-receptoneural junction. In the goldfish, the sacculus serves as an auditory organ. Furukawa & Ishii (28) first described the presence of excitatory postsynaptic potentials (EPSPs) in the VIII nerve. The EPSP preceded the generation of the action potential. Later publications were devoted to characterizing the postsynaptic responses to acoustic stimulation. Furukawa et al (27) studied the time-course of the postsynaptic potentials in response to sinusoidal acoustic stimuli.

In the same paper, the authors report observing spontaneous miniature excitatory postsynaptic potentials (mEPSP). Most of the mEPSPs were of shorter duration than most of the EPSPs. The authors propose that the EPSP is composed of a number of mEPSPs evoked with a slightly different timing. Finally, the authors cooled the preparation and found that the synaptic delay was markedly increased, while an increase in the duration of the EPSP was less marked.

Ishii et al (29) applied a Poisson analysis to the EPSPs in the goldfish VIII nerve. In their studies, Ishii et al (29) reduced the EPSP size by reducing the intensity of the acoustic stimulus. With the application of weak sounds, the EPSPs showed marked fluctuations in size. Even weaker sounds showed more marked fluctuations. The fluctuations of EPSP size at the neuromuscular junction that result when the concentrations of calcium and/or magnesium are altered have been shown to obey Poisson's law, indicating that the EPSP is formed from a large number of contributing units. The Poisson relation was found to be applicable to the EPSPs of the VIII nerve of the goldfish in response to weak sounds, although discrepancies were found in its application to the EPSPs resulting from a strong acoustic signal. The authors conclude that transmission between the hair cells and the VIII nerve involves quantal release of transmitter.

Thus, the hypothesis that there is a chemically-mediated component to hair cell-VIII nerve transmission has been unequivocally demonstrated on electrophysiological grounds. Whether or not the findings of Furukawa et al (27) in the goldfish VIII nerve will be applicable to the organ of Corti remains to be seen. But anatomical evidence points to the similarity of synaptic structure in all hair cell-receptoneural synapses and it would thus seem that such characterizations might be universally applicable to the hair cell-receptoneural junction.

Pharmacology of the Afferent Synapse

A number of chemical substances have been proposed, with little evidence, to be the transmitter released by the hair cell in response to sensory stimulation. In order to prove that a given substance is a transmitter at a chemically-mediated synapse, it is generally considered necessary to fulfill the following criteria: (*a*) it must be demonstrated that the presynaptic cell of a given synapse is capable of synthesizing the putative transmitter; (*b*) a mechanism of storage of the putative transmitter substance must be demonstrated; (*c*) a mechanism of termination of action of the putative transmitter should be demonstrated; (*d*) administration of the putative transmitter substance should mimic the action of presynaptic stimulation; (*e*) pharmacologic agents should have the same effect on applied putative transmitters and on presynaptic stimulation as agents known to interfere with, or mimic, the action of the putative transmitter may be expected to interfere with exogenously administered transmitter or presynaptic stimulation; and most importantly, (*f*) it must be shown that the putative transmitter is released during presynaptic stimulation.

In investigations into the identity of the afferent transmitter (the transmitter released by the hair cells in response to sensory stimulation) the tacit assumption is made that all hair cells of the acousticolateralis system release the same transmitter. Such an assumption is based upon the common evolutionary origin of these organs. But the applicability of any given finding must be tempered with an acknowledgement of the possibility that there may be species differences in the identity of the afferent transmitter and that synapses exhibiting differential structural characteristics may utilize different transmitters. In addition, in the interpretation of pharmacological data obtained from the cat and guinea pig, it is important to note that any effects of drugs or putative transmitters on the compound action potential (CAP) probably reflect the effects of those agents upon the synapses of the inner hair cells, since 95% of the afferent fibers in the cat innervate the inner hair cells (30) and 85 to 90% of the afferent fibers in the guinea pig innervate the inner hair cells (31). It is possible that there

may be distinct differences in receptor (pharmacological) sensitivity or in transmitter release mechanisms between the inner and outer hair cells. The data of Gulley & Reese (13), discussed earlier, suggest that the macromolecular configuration of the postsynaptic receptor, and consequently, perhaps its susceptibility to stimulation or blockade by agonists and antagonists, may differ in the synapses serving inner and outer hair cells.

The criteria which must be met before acceptance of a particular substance as the afferent transmitter have not been met for any chemical substance at the present time. On the contrary, most substances have been eliminated as likely transmitter candidates at this synapse. The evidence favoring or eliminating transmitter candidates at the afferent synapse follows.

GAMMA-AMINOBUTYRIC ACID (GABA) A great deal of research has been performed examining the possibility that GABA may be the transmitter released by sensory hair cells. The evidence ranges from examination of the ability of acoustico-lateralis structures to synthesize GABA (32–35); to the presence of GABA in auditory structures (34–37); to the effect of administered GABA (38–40, 44), or GABA antagonists (38, 41–43) on acoustico-lateralis electrical activity; and to the effect of agents interferring with GABA synthesis (38, 48) or degradation (34, 45–47). This evidence is extensively discussed by Guth et al (49) and when all the evidence is weighed it is apparent that GABA is probably not the afferent transmitter.

CATECHOLAMINES Support for the idea that the afferent transmitter is a catecholamine comes from only one laboratory. This support is in the form of changes in the diameter and electron density of the synaptic body of frog vestibular hair cells following treatment with agents known to affect afferent catecholamine storage such as reserpine, guanethidine, and monoamine oxidase inhibitors (17, 34, 50). On the other hand, neither the rabbit's (51) nor the cat's (52) organ of Corti (Figure 1) show positive histofluorescence for catecholamines. Neither reserpine nor 5-, or 6-hydroxydopamine produced changes in the afferent cochlear synapse of the rabbit (9). It may be that the blood-perilymph barrier is better developed in the rabbit than in the frog and so the drugs used had access to the frog labyrinth but not that of the rabbit. It is also possible that the transmitter is a nonfluorescent monoamine.

Neither neurochemical (32) nor pharmacological (39, 53, 54) evidence supports the notion that a catecholamine is the primary afferent transmitter. For more extensive discussion of the transmitter role of catecholamines see Guth et al (49).

SEROTONIN (5-HYDROXYTRYPTAMINE) With even more certainty than in the case of the catecholamines it may be said that the evidence does not favor serotonin as the primary afferent auditory transmitter. Both the neurochemical (32) and the histofluorescent (9, 51, 52) data are negative. The cochlear infusions of serotonin antagonists fail to influence cochlear electrical activity in ways referable to the specific antagonism of serotonin (55–59). Intracochlear instillation of serotonin itself caused a decrease in the compound action potential (CAP) of guinea pig (39) but only at very high concentrations. However, intracochlear instillation in the cat produced no change in cochlear electrical activity (55). Again, for more extensive discussion see Guth et al (49).

ACETYLCHOLINE (ACh) While there is reliable evidence that ACh is the neurotransmitter released by the efferent or olivocochlear endings of the cochlea (60–62) there is little support for the suggestions (63–65) that ACh also mediates afferent transmission. In fact, there is evidence which weighs against such a role for ACh. Acetylcholinesterase has been found to be associated primarily with the efferent or olivocochlear bundle (66), and not with hair cells or afferent dendrites. Likewise, Jasser & Guth (67) have shown that choline acetyltransferase, the enzyme which synthesizes ACh, is associated with the efferent or olivocochlear bundle and not the afferent synaptic structures. Similarly, Godfrey et al (68) measured choline acetyltransferase and acetylcholinesterase activities in cochlea and came to the same conclusion. Fex & Wenthold (33) also measured cholineacetyltransferase activity in cochlea and agreed with the conclusions of Jasser & Guth (67) and Godfrey et al (68).

Other neurochemical (32) and pharmacological evidence (69–76) supports a role for ACh as the efferent but not the afferent transmitter. For more extensive discussion see Guth et al (49).

GLYCINE The available evidence indicates that glycine is not the afferent transmitter in the cochlea. Neither neurochemical (35) nor pharmacological studies (38–40) support any role for glycine in the cochlea.

ASPARTATE AND GLUTAMATE Several investigators have suggested that aspartate or glutamate might be the primary auditory afferent transmitter (39, 40, 75, 77). In all these instances, glutamate or aspartate in millimolar concentrations caused an increase in firing rate of afferent auditory neurons when instilled intracochlearly. These amino acids are known to cause such an excitatory effect practically everywhere in the nervous system (78). No other evidence supports glutamate's or aspartate's transmitter role in the cochlea. Godfrey and co-workers (35) found glutamate to be high in

sensory as well as nonsensory portions of the cochlea and the aspartate concentration was graded from cochlear apex to base, a distribution not consonant with a presumed role as afferent transmitter. As will be seen later, evidence is much stronger for a transmitter role of these amino acids in the cochlear nucleus (Figure 1). Furthermore, it might be expected, as has been shown for ACh following olivocochlear bundle stimulation (76), that transmitters would appear in the fluid bathing the afferent synapse, the perilymph, following acoustic stimulation. Sewell et al (79) found no such increase in either aspartate or glutamate concentration in perilymph following acoustic stimulation.

Gulley et al (79a) determined the distribution of putative transmitters autoradiographically in the organ of Corti. Although some cochlear structures such as efferent fibers and endings showed labeling following incubation with glutamate and aspartate, inner and outer hair cells did not. Excitatory amino acid receptors have been differentiated into *N*-methyl-D-aspartate-preferring and non-*N*-methyl-D-aspartate-preferring at least partly based on the ability of DL-α-amino adipate to block the former receptor. Fex & Martin (79b) applied DL-α-amino adipate intracochlearly and found no alteration in cochlear electrical activity. The case for either glutamate or aspartate as the primary afferent transmitter of audition must be said to be "not proven." A wider ranging discussion of this subject is available (49).

MISCELLANEOUS TRANSMITTER CANDIDATES

(Histamine, taurine, substance P, adenosine triphosphate, prostaglandin, tyramine) Histamine was not detected in the organ of Corti using a fluorescent histochemical technique (80). Intracochlear infusion of histamine in the guinea pig at 10 mM produced only a slight decrease (19%) in the CAP (39). It would appear, then, that histamine is probably not a candidate to be the afferent transmitter. Taurine, when instilled intracochlearly in the guinea pig (39), did not affect the CAP or the CM at 10 mM. Substance P did not affect the CAP or the CM when administered intracochlearly in the guinea pig (42). While adenosine triphosphate (ATP) reduced the CAP 38 and 95% when administered intracochlearly at concentrations of 1 and 10 mM, respectively, the effects were attributed to ATP's ability to chelate calcium (39).

Intraarterial injection of prostaglandin E_1 (PGE_1) in the cat was found to produce an increase in the amplitude of the CAP, as well as blockade of efferent stimulation effects (81). When administered intracochlearly in the guinea pig (39), PGE_1, PGA_1, PGE_2, PGF_2, and $PGF_{2\alpha}$ all produced

depression of the CAP when infused at 1 mM concentrations. Because salicylate, a prostaglandin synthesis inhibitor, also reduces the CAP when applied intracochlearly, Bobbin & Thompson (39) suggest that the prostaglandins may play a regulatory role in afferent synaptic transmission.

While octopamine was without effect during intracochlear infusion of 10 mM in the guinea pig, tyramine produced, at 1 and 10 mM concentrations, 2 and 94% reductions, respectively, in the CAP (39). The authors suggest that the data indicate that tyramine may be a transmitter candidate in the cochlea.

TRANSMITTER-LIKE ACTIVITY (TLA) OR AUDITORY NERVE ACTIVATING SUBSTANCE (ANAS) Amongst ourselves we call it the transmitter." When strangers are present, we call it, with a wink, "Transmitter-like Activity" (TLA). In print, it is called "Auditory Nerve Activating Substance" (ANAS) (79). ANAS is detectable by bioassay in the bullfrog (*R. catesbeiana*). It appears in the perilymph of guinea pigs or bullfrogs during sound stimulation of these animals and causes an increase in the firing rate of single units in the frog auditory nerve (79). The perilymph of animals maintained in quiet has no detectable ANAS. It appears to be stable in the frozen state over several days. It has thus far eluded detection by standard physical means, probably because of its low concentration in perilymph.

Since none of the standard pharmacological blocking agents tried (see above) affect primary afferent auditory transmission and since none of the standard transmitters considered above fit this role, it may be that the primary afferent transmitter of audition is of an entirely novel structure.

EFFERENT TRANSMISSION IN THE COCHLEA

Autonomic

A majority of workers concur that the cochlea receives two sets of sympathetic fibers, one set innervating blood vessels and the other independent of blood vessels (82–86) and that these fibers arise from both the superior cervical and stellate ganglia. One group of investigators found only one set of adrenergic fibers and those innervated the branches of the labyrinthine artery only (87, 88).

The blood vessel-independent sympathetic terminals were found close to spiral ganglion cells of the myelinated type (89). They were also seen in the osseous spiral lamina above and below the myelinated afferent nerve fascicles. In the region of the habenula perforata adrenergic nerve terminals seemed to make direct contact with unmyelinated axons which were pre-

sumed to be afferent neurons. In seeking a role for the blood vessel-independent sympathetic innervation Spoendlin & Lichtensteiger (82, 83) referred to the work of Loewenstein (90) who demonstrated that sympathomimetic agents lower the thresholds of touch receptors. Santini (91) has demonstrated the existence of noradrenergic endings in the center of Pacinian corpuscles so that sympathetic activation could mediate changes in mechanoreceptor thresholds. The same role could be served by the nonvascular sympathetic fibers in the ear.

Ross has made the suggestion that the ear receives parasympathetic innervation as well (91a). It is further suggested that these parasympathetic fibers act to exert control over the adrenergic innervation of the inner ear. For further discussion see Guth et al (49).

Olivocochlear Innervation

The olivocochlear bundle (OCB) has both a crossed (COCB) and an uncrossed (UCOCB) component as originally described by Rasmussen (92). The cells of origin have been intensely studied by Warr & Guinan (93). The OCB takes origin from cells in the medial and lateral regions of the superior olivary complex as well as the lateral superior olivary nucleus, the medial and ventral nuclei of the trapezoid body, and the dorsomedial periolivary nucleus (93). The majority of COCB neurons arise in the medial region of the superior olivary complex, the medial nucleus of the trapezoid body, and the dorsomedial periolivary nucleus and end primarily on outer hair cells. The UCOCB arises primarily in the lateral superior olivary nucleus and the lateral region of the superior olivary complex and end under inner hair cells either on the cells or on the afferent dendrites serving them.

The COCB crosses the midline at the floor of the fourth ventricle and as it passes the cochlear nuclei (Figure 1) gives off collateral fibers which travel to the anterior ventral cochlear nucleus. The COCB and UCOCB eventually come together as they proceed to their terminations in the organ of Corti. Beneath the inner and outer hair cells the OCB endings are large and filled with spherical electron-lucent synaptic vesicles. There are also interesting suggestions (94, 95) that OCB fibers and non-OCB, cholinesterase-positive fibers (94a) may end on supporting cells (Figure 1). More extensive discussions of the anatomy of the OCB are available (2, 62).

Tetanic electrical stimulation of the COCB causes a reduction in amplitude of the VIII nerve compound action potential (CAP) (96) and so it is generally assumed that the OCB is inhibitory. Fex (97) was the first to note that electrical stimulation of the COCB caused an augmentation of the hair cell A-C potential, also called the cochlear microphonic. Fex (98) also first demonstrated that the efferent nerve fibers in both the COCB and UCOCB

are activated to discharge in response to sound. However, no change in cochlear potentials has been recorded subsequent to such "physiological" stimulation of the OCB.

The relatively limited number of behavioral investigations, with their widely variant techniques and results, do not permit a definitive statement as to the function of the efferent system in physiological auditory signal processing. However, the weight of evidence tempts one to suggest that the olivocochlear nerves may influence signal-to-noise ratios at or near threshold to improve the reception of low intensity sounds. This suggestion is supported by the work of Dewson (99), Trahiotis & Elliott (100) and Borg (101).

There is an extensive review of the pharmacology of the OCB (62). For the more limited purposes of this article it may suffice to say that the criteria which must be fulfilled before a substance is accepted as the neurotransmitter have been largely fulfilled for ACh as the transmitter released from COCB endings in the cochlea. The evidence is as follows:

1. Choline acetyltransferase activity has been found in cochlea and it is generally agreed that it is associated with the OCB (33, 67, 68).
2. ACh itself has not been demonstrated in OCB endings, largely because no methods yet exist capable of such demonstration, but OCB endings are heavily endowed with electron-lucent, spherical synaptic vesicles of a size seen at other cholinergic junctions (11).
3. ACh-like activity has been shown to increase in cochlear perilymph coincident with COCB stimulation (76).
4. The intracochlear application of exogenous ACh plus eserine on cochlear potentials mimics the effect of OCB stimulation (69, 70, 102).
5. The application of many drugs known to interact with ACh at other sites produce the predicted response of the COCB-hair cell synapse (49). These drugs include hemicholinium-3, gallamine, *d*-tubocurarine, atropine, hexamethonium, strychnine, brucine, coniine, and tetanus toxin (49).
6. Acetylcholinesterase, as the agency responsible for terminating the action of transmitter ACh, has been shown to be associated with the OCB by many investigators (reviewed in 103).

Thus it is generally accepted that ACh is the transmitter released at least by the crossed olivocochlear bundle. The ACh receptor on the hair cells opposite the OCB endings is apparently different from the standard ACh receptor in that it appears about equally well blocked by strychnine, *d*-tubocurarine, and atropine. Of these, only strychnine acts following systemic application. It is also nonstandard in that, while α-bungarotoxin will

antagonize the effects of OCB stimulation, that antagonism is reversible unlike that seen at the neuromuscular junction (104).

The Dale-Eccles credo that one nerve likely releases only one transmitter was dealt yet another blow by the report by Fex & Altschuler (105) of the presence of enkephalin-like immunoreactivity associated with OCB endings in the cochlea. As if the cochlea were not already oversupplied with transmitters, Lim et al (106) reported the presence of vasoactive intestinal peptide in the perilymph of chinchillas.

The variety of junctions in the cochlea now includes the sympathetic adrenergic efferents, the cholinergic efferents of the OCB, the inner and outer hair cell receptoneural junctions, reciprocal afferent synapses, and a dendrodendritic site. All these packaged in an accessible chamber conveniently arranged for perfusion, electrophysiological recording, or biochemical studies.

TRANSMITTERS OF THE COCHLEAR NUCLEUS

As compared with the cochlea, the problem of correlating specific transmitters with specific cell types or aggregates in a structure as complicated and heterogeneous as the cochlear nucleus (Figure 1) is much more difficult but not impossible with the techniques of the day. Only in the last few years have scientists interested in transmission turned their attention to this challenging task in this important auditory structure. The purpose of this subchapter is to inform the interested reader of the studies which have attempted to understand the distribution of transmitters in the cochlear nucleus. The only attempts in this review at correlating the complicated anatomy, physiology, and transmitter distributions will be *en passant* and are not meant to be comprehensive.

Glutamate and Aspartate

The leading candidates for the role of secondary auditory transmitter (i.e. the transmitter released by VIII nerve endings in the cochlear nucleus) are glutamate and aspartate (107, 108). Following cochlear ablation in the guinea pig, the concentrations of both amino acids decreased in the ventral cochlear nucleus (a primary area receiving VIII nerve endings) but not in the superficial dorsal cochlear nucleus (an area receiving few or no VIII nerve endings). The decrease in concentration of aspartate followed the degeneration of VIII nerve endings with greater fidelity than the decrease in the concentration of glutamate. The close relation between the time-course of decrease of aspartic acid in the cochlear nucleus and the morpho-

logical degeneration of the VIII nerve terminals after cochlear ablation suggests that aspartic acid may be concentrated in the terminals of the auditory nerve. The time-course of the decrease of glutamic acid and the continued slow decrease occurring after most primary terminals had degenerated suggests a secondary role for it.

In an extension of this work, Wenthold (108) subdivided the cochlear nucleus into seven anatomical regions and repeated the procedures of amino acid determinations in these regions following cochlear ablation. In this study, the distribution of aspartic acid fit that of a putative transmitter better than the distribution of glutamic acid. Glutamic acid concentration was relatively uniform throughout the areas sampled. This finding confirms the results of Godfrey et al (109–111). According to both Wenthold (108) and Godfrey et al (109) aspartate showed a less uniform distribution among cochlear nucleus subdivisions. As a further test for the suggestion that glutamate might be the transmitter released by VIII nerve endings in the cochlear nucleus, Bird et al (112) injected kainic acid into the brainstem roughly equidistant from the anteroventral, posteroventral, and dorsal cochlear nuclei. Kainic acid is felt to destroy glutamatoceptive neurons somewhat specifically. The rate and extent of degeneration produced correlated with the distribution of VIII nerve terminals supporting the hypothesis that glutamate may be the transmitter at these sites. As pharmacologists, it may be permitted the comment that kainic acid is only relatively specific, such specificity depending on its concentration.

Wenthold (114) studied the high K^+-depolarization-induced release of amino acids from cochlear nucleus slices in the presence and absence of calcium and with the auditory nerve intact or degenerated. He concluded on the basis of the quantitative effects of nerve lesion and calcium on amino acid release that glutamate is a more likely candidate than aspartate for the transmitter released by the auditory nerve. Canzek's & Reubi's findings (115) are essentially in agreement with those of Wenthold (114). Hansson et al (116) were able to demonstrate a sound-stimulation induced increase in amounts of glutamate and aspartate collected from the surface of the cochlear nucleus.

Enzymes associated with glutamate and aspartate metabolism, glutaminase and aspartate amino transferase, not only have high activities in the auditory nerve but their activities are most markedly diminished following denervation in the areas of cochlear nucleus associated with auditory nerve endings (117).

Martin & Adams (118) applied the excitatory amino acid antagonist, DL-α-amino adipate, to the cochlear nucleus iontophoretically and demonstrated antagonism of sound-induced excitation of certain units in the coch-

lear nucleus. They thus conclude that the transmitter of the auditory nerve may be glutamate or aspartate or both.

Glycine

Glycine levels in the cochlear nucleus are similar to those reported for spinal cord gray matter where it is presumed to be a transmitter. Godfrey et al (111) suggest that part of the glycine is associated with small cells that may be interneurons. Caspary et al (113) applied glycine iontophoretically to various areas of the cochlear nucleus and found either a generalized depression or a striking inhibition of activity with little reduction of driven neuronal firing. Iontophoretic application of strychnine, a glycine antagonist, caused a moderate enhancement of spontaneous and sound-induced single unit responses (113). Employing tritium labeled strychnine, Zarbin et al (113a) found moderate binding to what they termed "glycine receptors" in the dorsal cochlear nucleus.

Gamma-Aminobutyric Acid

The distributions of γ-aminobutyric acid (GABA) and associated enzymes also suggest a neurotransmitter role for this amino acid in the cochlear nucleus. Firstly, there is a striking range of values for GABA with the highest levels in the granular regions and dorsal cochlear nucleus (110), while the posteroventral cochlear nucleus has about 1/6–1/8 as much. GABA was also found to be in high concentration in dorsal cochlear nucleus and low in ventral cochlear nucleus by Tachibana & Kuriyama (119). These latter authors suggest that the dorsal cochlear nucleus may receive GABA-ergic neurons.

These authors (119) also studied the distribution of GABA transaminase (GABA-T) by histochemical means. The enzyme, felt to be an important means for terminating GABA's action, was found localized more in the dorsal cochlear nucleus than in the ventral cochlear nucleus, correlating with GABA's distribution.

In contrast, Davies (120) found that the most of the GABA-T containing cells were in the anterior ventral cochlear nucleus, although cells throughout the cochlear nucleus stained for this enzyme. He concluded that GABA might be the transmitter for pathways intrinsic as well as extrinsic to the cochlear nucleus. That GABA might function as an inhibitory transmitter in the cochlear nucleus was supported by the observation of Whitfield & Comis (121) that GABA produces a strong depression of firing rate when applied locally.

Caspary et al (113) likewise applied GABA iontophoretically onto cochlear nucleus neurons and recorded inhibition of both spontaneous and tone-evoked single unit activity.

The enzyme synthesizing GABA, glutamic acid decarboxylase (GAD), was found present in cochlear nucleus (122, 123) and auditory nerve (122). In a recent publication on the subject, Davies (123) has shown that both GAD and GABA seem to concentrate in the dorsal cochlear nucleus in rats, cats, and guinea pigs. Davies (123) also showed that sectioning the dorsal acoustic stria led to a significant (but less than total) decrease in GAD and GABA-T, while decochleation did not produce a lasting fall in enzyme activity. He concludes that about 30% of the GAD in the cochlear nucleus can be attributed to centrifugal fibers coursing through the dorsal acoustic stria and terminating in the dorsal cochlear nucleus. The remainder of GAD activity exists in nerve endings of intrinsic nerve fibers. Auditory nerve had very low GAD activity which did not change following cochlear lesions (122), suggesting that GABA is not the transmitter released by the auditory nerve.

Acetylcholine

Conclusions concerning specific distributions of cholinergic pathways are not to be had from the current literature. But it does appear that ACh may be a transmitter released from cells, intrinsic as well as extrinsic to the cochlear nucleus. The major extrinsic cholinergic pathways seem to be the collaterals of the crossed olivocochlear bundle and a separate excitatory pathway from the superior olivary complex ending in the ipsilateral anteroventral cochlear nucleus (124). Using hemicholinium-3, because of its known ability to inhibit ACh synthesis, Comis & Davies (124) determined the effect of this agent on ACh content of the cochlear nucleus after ipsilateral superior olivary stimulation. They found a marked reduction in ACh content of cochlear nucleus under these conditions and concluded that this pathway represented a major extrinsic source of cholinergic neurons. Furthermore, these authors (124) demonstrated a reduction in ACh content of the cochlear nucleus by sound stimulation in the presence of hemicholinium-3. Such a decrease only occurred with the superior olive intact. This finding provides evidence that the cholinergic innervation is centrifugal and not centripetal.

Acetylcholine (ACh) seems not to be the transmitter released by auditory nerve endings in the cochlear nucleus (122, 123). However, within the cochlear nucleus, the strikingly uneven distribution of acetylcholinesterase (AChE) (127) suggests another neurotransmitter role for ACh. AChE is known to be a less reliable indicator of the location of cholinergic neurons than is choline acetyltransferase (ChAc). Godfrey et al (126) therefore examined the cochlear nucleus for the distribution of both enzymes. The findings of Godfrey et al (126) of high AChE and ChAc activities in the

granular layer superficial to the anteroventral cochlear nucleus agree with Rasmussen's (127) report that most crossed olivocochlear fibers enter and terminate in this region. The especially high ChAc activity in the ventrolateral part of the granular layer superficial to the anteroventral cochlear nucleus agree with the findings of Osen & Roth (125) that AChE-positive fibers, presumably of the olivocochlear bundle, travel through the ventrolateral part of the cochlear nucleus and may end in the superficial layer of the dorsal cochlear nucleus (127). The release of ACh from dorsal cochlear nucleus upon olivocochlear bundle stimulation (128) would support such a projected path. More recently, Godfrey & Matschinsky (128a) mapped AChE and ChAT activities in the rat cochlear nucleus. The rat showed ChAT activities about 15 times higher than those in cat cochlear nucleus and with a generally more uniform distribution. Explanations for this quantitative difference are had by analogy with the difference between cat and rat retina or by suggesting a larger number of intrinsic cholinergic neurons or a larger number of centrifugal cholinergic neurons in the rat than in the cat.

Interestingly, Comis & Whitfield (129) have demonstrated by single unit studies that where ACh has an effect, when applied locally, it is invariably excitatory. This suggests that the olivocochlear endings exert opposite effects in the cochlea and cochlear nucleus. The olivocochlear collaterals (if true collaterals) to the cochlear nucleus would then be producing excitation while VIII nerve units would be simultaneously inhibited, a very interesting arrangement, perhaps suited for shaping of information.

In an interesting and circumspectly written paper Hunt & Schmidt (130) reported on the binding patterns of radio-iodinated α-bungarotoxin in the rat central nervous system. These authors studied the distribution of the toxin radioautographically. It was presumed that α-bungarotoxin exhibited a certain specific affinity for cholinoceptive sites in the central nervous system. This concept has been questioned (131) and Hunt & Schmidt go to great lengths to present a balanced view of their results. All these caveats notwithstanding, they (130) found quite high concentrations of silver grains over the cochlear nucleus, particularly the ventral cochlear nucleus. The source of the prejunctional (presumed) cholinergic nerves serving the toxin binding site can only be guessed at. However, it is parsimonious to assume that these might be intrinsic as well as olivocochlear and ipsilateral olivary cholinergic inputs to the cochlear nucleus.

Employing a radiolabeled muscarinic antagonist, quinuclidinyl benzilate (QNB), Wamsley et al (130a) mapped the distribution of so-called muscarinic cholinergic receptors in rat brainstem. These researchers found high levels of autoradiographic grains over the dorsal and ventral cochlear nuclei. In fact, they report the presence of discontinous bands of autoradio-

graphic grains associated with the granule cell layer which cells are thought to receive olivocochlear collateral fibers. Contrariwise, Rotter et al (130b), using an irreversible muscarinic antagonist, Propylbenzilylcholine mustard (PrBCM), as their radioligand found low and very low densities of so-called muscarinic receptors in dorsal and ventral cochlear nuclei, respectively.

Pickles & Comis (132) and Pickles (133) have studied the influence of atropine applied to the dorsal surface of the cochlear nucleus on behavioral responses to sound stimuli. They found that the ability to detect an auditory signal in noise is impaired following the application of atropine while the absolute threshold is much less affected. In the latter paper, Pickles (133) points out that atropine increases the width of the critical band. He plumps for the ipsilateral cholinergic pathway (arising in the superior olivary complex) rather than the olivocochlear bundle or an intrinsic cholinergic synapse as the site of atropine's action.

Catecholamines

The cochlear nucleus also receives a significant projection of noradrenergic neurons (134, 135). Versteeg & co-workers (135a) found both norepinephrine and dopamine present in the combined dorsal and ventral cochlear nuclei, dopamine being in very low concentration as it is in most areas of the pons and medulla. The norepinephrine-containing fibers reach the cochlear nucleus by two distinct pathways. One pathway enters through the dorsal region of the anteroventral cochlear nucleus and the second enters the dorsal and posteroventral cochlear nucleus via the dorsal acoustic stria. At least some of these fibers originate from the locus coeruleus. Stimulation of the locus coeruleus caused a reduction in spike generation of neurons in the dorsal cochlear nucleus (135b). Treatment with reserpine did away with the ability of the locus coeruleus stimulation to cause inhibition and intraventricular norepinephrine reinstituted the inhibition (135b).

The local application of norepinephrine to the cochlear nucleus (136) leads to inhibition of single unit activity. Pickles (137), in a companion piece to his previous work employing atropine, applied norepinephrine directly to the surface of the cochlear nucleus. In this study, norepinephrine was found to increase both the absolute and the masked thresholds significantly, affecting both to the same extent. The influence of wideband noise masking was greater than that of narrowband masking after norepinephrine application, leading Pickles (137) to suggest that, as with atropine, norepinephrine had increased the width of the critical band.

Other Amines

Histamine (H_1) receptors, as defined by ^{3}H-mepyramine binding and autoradiography, were found throughout the auditory system (138a). Al-

though grain densities were not very high in the dorsal and ventral cochlear nuclei, they were present. Taurine was also reported to be present in cochlear nuclei but in relatively low concentrations (138b). Fuxe (138) has reported the presence of serotonergic nerve endings in the dorsal cochlear nucleus.

Polypeptides

Four polypeptides with presumed transmitter roles have been found present in the cochlear nucleus, substance P, neurotensin, enkephalin, and somatostatin.

Substance P is an undecapeptide which has been nominated as the transmitter of primary afferent transmission in the spinal cord (139). In an extensive investigation of the distribution of substance P-like immunoreactivity in the central nervous system of the rat, Ljungdahl et al (140) found substance P positive cell bodies and nerve terminals in many areas of the rat central nervous system. A few substance P-like immunoreactive cell bodies were found in the dorsal cochlear nucleus but none in the ventral cochlear nucleus. Likewise only a few cell bodies and nerve terminals were found positive for neurotensin and then only in the dorsal cochlear nucleus of all auditory areas studied (140a).

Somatostatin also has been found to be present in cochlear nucleus by radioimmunoassay (141) and immunohistochemistry (142).

Enkephalin-like immunoreactivity was detected immunohistochemically in cell bodies and processes in the dorsal and ventral cochlear nuclei (143). "Opiatergic" receptors, as defined by ^{3}H naloxone autoradiography, have been found in the molecular layer of the dorsal cochlear nucleus (144).

Any attempts at summarizing these data can only lay the author open to serious charges of oversimplification. Nonetheless, by way of attempting some sorely-needed clarification here is a summary.

1. The transmitter released by the auditory nerve in the cochlear nucleus is unlikely to be: ACh, GABA, glycine, or a catecholamine. It might be glutamate or aspartate, with aspartate receiving somewhat stronger evidential support for this role.
2. GABA seems to be involved as both an extrinsic and intrinsic transmitter.
3. Cholinergic neurons investing the cochlear nucleus arise from the olivocochlear bundle and the ipsilateral bundle arising in the superior olivary complex. There may be intrinsic cholinergic neurons but there seem to be few, if any, cholinergic neurons projecting from the cochlear nucleus (126).

4. Noradrenergic neurons investing the cochlear nucleus arrive in two bundles. At least some of the noradrenergic fibers arise from the locus coeruleus.
5. The function of most of these transmitters is unknown. However, ACh seems generally excitatory while norepinephrine, GABA, and glycine are generally inhibitory. An atropine-sensitive (cholinergic) pathway and a noradrenergic pathway seem important for the detection of signals in noise.

TRANSMITTERS OF HIGHER AUDITORY CENTERS

First, some caveats (Table I):

1. In their review of the subject Oswald & Freeman (156) say that no effect of α-bungarotoxin on synaptic transmission has been observed in the mammalian central nervous system and, "the question of whether α-bungarotoxin binds to the CNS nicotinic acetylcholine receptor has not been fully resolved."
2. The use of ^{3}H-strychnine to delineate glycine receptors is suspect. In this publication Zarbin et al (113a) report that strychnine is displaced almost as easily by β-alanine as it is by glycine and that not all other ligands have been examined by their abilities to displace strychnine. For instance, strychnine antagonizes ACh at the COCB-hair cell junction.
3. In their paper using ^{3}H-mepyramine to delineate H_1-histamine receptors, Palacios et al (138a) discuss the pitfalls of their method. For example, not all H_1 receptors are neuronal. Furthermore, although mepyramine is among the most specific antihistaminics, it is well known that antihistaminics do antagonize agonists other than histamine. It might have been more circumspect to entitle this paper, "Mepyramine binding sites."
4. A correlation was suggested (130a) between H_1 binding sites and muscarinic sites. This correlation appears to break down in the superior olive and nucleus of the lateral lemniscus.
5. There are few or no monoamine cell bodies or varicosities (52, 152) in the superior olive. Therefore, the observation that phentolamine increases glucose utilization in this structure (147) must be explained by an effect of the drug at some site outside the olive and presynaptic to it.

The information contained in Table 1 is insufficient for any broad-brush correlations. It is presented as a means for indicating the state of neurochemical information in the auditory system and to demonstrate again what a fertile field audition and sensation in general may be for pharmacologists in the future.

Table 1 Transmitters of higher auditory centers

	Acetylcholine (ACh)	Histamine	Monoamines	Amino acids	Peptides
Superior olive	No QNB[a] (130a) $^{+++}\alpha$-BuTx[a] (130) Highest ChAT in auditory	Moderate mep. binding (138a)	No 5-HT, DA, or NE in OCB neurons (52) No monoamine cell bodies or varicosities (152)	Low GABA and GAD (138b) Avg. glutamate and taurine (138b) Sensitive to kainate (154) High glycine receptor (113a)[c]	SRIF neurons and fibers (142) (lat. trapezoid nucleus, few ELI fibers and neurons (143)
Nucleus lateral lemniscus	Very high QNB[a] (130a) $^{++}\alpha$-BuTx[a] (130) High PrBCM[a] (130b)	Low-moderate mep binding (138a)	DBH-containing soma and fibers (135) Phentolamine → ↑ glucose[b] (147)	High "glycine" receptor (113a)[c]	SRIF neurons and fibers (142) traceable to inferior colliculus
Inferior colliculus	High QNB[a] (130a) $^{+++}\alpha$-BuTx[a] (130) Intermediate PrBCM[a] (130) ACh, eserine → excitation atropine → inhibition (154)	Low mep. binding in caudal portion (138a)	Adrenergic fibers from locus coeruleus (135, 151) Low NE, DA content (135a) 5-HT neurons and endings (152, 153) Phentolamine → ↑ glucose[b] (147)	High GABA (148) and GAD (148, 150) GABA, glycine → ↑ activity (149) Picrotoxin → ↓ response to sound (149) Moderate glycine (150) Low "glycine" receptor (113a)[c]	SRIF neurons and fibers (142) Few ELI perikarja (143) Low VIP (146)

Medial geniculate	Low PrBCM[a] (130b)		Adrenergic fibers from locus coeruleus (151) Moderate no. DBH neurons (135) 5-HT neurons and endings (152, 153) Phentolamine → sm. ↑ glucose[b] (147)	High GABA and GAD (138b) High taurine (138b) Taurine inhibitory (155)	Many SRIF fibers, few neurons (142) Low VIP (146)
Auditory cortex	Moderate α-BuTx[a] (130) ACh release following medial geniculate stimulation (145)	Moderate mep. binding (138a)	Phentolamine → no change in glucose[b] (147)	No "glycine" receptors (113a)[c]	SRIF neurons and fibers (142) ELI in basket cells (143) High VIP (146)

[a] Binding
[b] Utilization
[c] Glycine receptors as defined by ^{3}H-strychnine binding

Abbreviations: α-BuTx, α-bungarotoxin, a nicotinic ligand; ChAT, choline acetyltransferase, the enzyme synthesizing acetylcholine; DA, dopamine; DBH, dopamine-β-hydroxylase-enzyme used as marker for catecholamine neurons; ELI, Enkephalin-like immunoreactivity; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase, the enzyme synthesizing GABA; 5-HT, 5-hydroxytryptamine (serotonin) mep., H^3-mepyramine, an H_1 histamine antagonist used as ligand; NE, norepinephrine; PrBCM, propylbenzylilcholine mustard, an irreversible muscarinic antagonist used as ligand; QNB, quinuclidinyl benzilate, a muscarinic antagonist used as ligand; SRIF, somatostatin reactive immunofluorence; and VIP, vasoactive intestinal peptide.

Literature Cited

1. Guth, P. S., Norris, C. H., Bobbin, R. P. 1976. The pharmacology of transmission in the peripheral auditory system. *Pharmacol. Rev.* 28:95–125
2. Klinke, R., Galley, N. 1974. Efferent innervation of vestibular and auditory receptors. *Physiol. Rev.* 54:316–57
3. Norris, C. H., Guth, P. S. 1974. Release of acetylcholine by the crossed olivocochlear bundle. *Acta Oto-Laryngol.* 77:318–26
4. Rossi, G., Voena, G., Cortesina, G., Buongiovanni, S. 1964. Changes in the cochlear microphonic potential due to resection of the efferent cochlear fibers. *J. Acoust. Soc. Am.* 36:1845–49
5. Smith, C. A., Sjöstrand, F. 1961. A synaptic structure in the hair cells of the guinea pig cochlea. *J. Ultrastruct. Res.* 5:184–92
6. Smith, C. A., Sjöstrand, F. S. 1961. Structure of the nerve endings on the external hair cells of the guinea pig cochlea as studied by serial section. *J. Ultrastruct. Res.* 5:523–56
7. Kikuchi, K., Hilding, D. 1965. The development of the organ of Corti in the mouse. *Acta Oto-Laryngol.* 60:207–22
8. Engström, H., Ades, H. W. 1973. *The Ultrastructure of the Sensory Organs.* New York: Elsevier. 318 pp.
9. Borg, E., Densert, O., Flock, A. 1974. Synaptic vesicles in the cochlea. *Acta Oto-Laryngol.* 87:321–32
10. Dunn, R. A., Morest, D. K. 1975. Receptor synapses without synaptic ribbons in the cochlea of the cat. *Proc. Natl. Acad. Sci. USA* 72:3599–603
11. Spoendlin, H. 1966. The organization of the cochlear receptor. *Fortschritte der Hals-Nasen-Ohrenheilkunde Fasc. 13.* 227 pp.
12. Rodriguez-Echandria, E. L. 1967. An electron microscopic study on the cochlear innervation. I. The receptoneural junction at the outer hair cell. *Z. Zellforsch. Mikrosk. Anat.* 78:30–46
13. Gulley, R. L., Reese, T. S. 1977. Freeze fracture studies on the synapses in the organ of Corti. *J. Comp. Neurol.* 171:517–44
14. Sjöstrand, F. S. 1958. Ultrastructure of retinal and rod synapses of the guinea pig as revealed by three dimensional reconstructions from serial sections. *J. Ultrastruct. Res.* 2:122
15. Wurtman, R. J., Axelrod, J., Kelly, D. 1968. *The Pineal.* London/New York: Academic. 199 pp.
16. Jepson, P. H. 1969. Studies of the structure and innervation of taste buds. *Acta Oto-Laryngol.* 55:1–32
17. Osborne, M. P., Thornhill, R. A. 1972. The effect of monoamine depleting drugs upon the synaptic bars in the inner ear of the bullfrog. (Rana catesbeiana). *Z. Zellforsch Mikrosk. Anat.* 127:347–55
18. Mullinger, A. M. 1964. The fine structure of ampullary electric receptors in Amirus. *Proc. R. Soc. London* 160: 345–59
19. Gray, E. G., Pease, H. L. 1970. On understanding the organization of retinal receptor synapses. *Brain Res.* 35: 1–15
20. Takasaka, T., Smith, C. A. 1971. The structure and innervation of the pigeon's basilar papilla. *J. Ultrastruct. Res.* 35:20–65
21. Hama, K., Saito, K. 1974. Tubular network in the sensory hair cell of the saccular macula of the goldfish: A hypothesis on the regulatory mechanism in the turnover of the synaptic vesicle membrane. *Gunma Symp. Endocrinol.* 11: 15–18
22. Tachibana, M., Morioka, H. 1976. Well developed gap junctions between Dieters' cells of the organ of Corti. *J. Electron Microsc.* 25:95–97
23. Iurato, S., Franke, K., Luciano, L., Wermbter, G., Pannese, E., Reale, E. 1976. Intracellular junctions in the organ of Corti as revealed by freeze fracturing. *Acta Oto-Laryngol.* 82:57–59
24. Gulley, R. L., Reese, T. 1977. Regional specialization of the hair cell plasmalemma in the organ of Corti. *Anat. Rec.* 189:109–24
25. Yamanda, Y. 1973. Fine structure of the ordinary lateral line organ. *J. Ultrastruct. Res.* 43:1017

25a. Nadol, J. B. Jr. 1980. Reciprocal synapses at the base of outer hair cells in the organ of Corti of man. *Ann. Otol. Rhinol. Laryngol.* 90:12–17

26. Bodian, D. 1978. Synapses involving auditory nerve fibers in primate cochlea. *Proc. Natl. Acad. Sci. USA* 75:4582–86
27. Furukawa, T., Ishii, Y., Matsuura, S. 1972. Synaptic delay and time course of postsynaptic potentials at the junction between the hair cells and VII nerve fibers in the goldfish. *Jpn. J. Physiol.* 22:617–35
28. Furukawa, T., Ishii, Y. 1968. Neurophysiological studies of hearing in goldfish. *J. Neurophysiol.* 30:1377–1403
29. Ishii, Y., Matsuura, S., Furukawa, T. 1971. Quantal nature of transmission at

the synapse between the hair cells and VIII nerve fibers. *Jpn. J. Physiol.* 21:79–89
30. Spoendlin, H. 1972. Innervation densities of the cochlea. *Acta Oto-Laryngol.* 73:235–48
31. Morrison, D., Schindler, R. A., Wersäll, J. 1975. A quantitative analysis of afferent innervation of the organ of Corti in the guinea pig. *Acta Oto-Laryngol.* 79:11–23
32. Flock, Å., Lam, D. M. K. 1974. Neurotransmitter synthesis in inner ear and lateral line sense organs. *Nature* 249:142–44
33. Fex, J., Wenthold, R. 1976. Choline acetyltransferase, glutamate decarboxylase, and tyrosine hydroxylase in the cochlea and cochlear nucleus of the guinea pig. *Brain Res.* 109:575–85
34. Monaghan, P. 1975. Ultrastructural and pharmacological studies on the afferent synapse of lateral line sensory cells of the African clawed toad, Xenopus laevis. *Cell Tissue Res.* 163:239–47
35. Godfrey, D. A., Carter, J. A., Berger, S. J., Matschinsky, F. M. 1976. Levels of putative transmitter amino acids in the guinea pig cochlea. *J. Histochem. Cytochem.* 24:468–72
36. Tachibana, M., Kuriyama, K. 1974. Gamma-aminobutyric acid in the lower auditory pathway of the guinea pig. *Brain Res.* 69:370–74
37. Thalman, R., Miyoshi, T., Kusasari, J., Ise, I. 1975. Normal and abnormal energy metabolism of the inner ear. *Otolaryngol. Clin. North. Am.* 8:313–34
38. Bobbin, R. P., Guth, P. S. 1970. Evidence that gamma-amino butyric acid is not the inhibitory transmitter at the crossed olivo-cochlear bundle-hair cell junction. *Neuropharmacology* 9:567–74
39. Bobbin, R. P., Thompson, M. H. 1978. Effects of putative transmitters on afferent cochlear transmission. *Ann. Otol. Rhinol. Laryngol.* 87:185–90
40. Klinke, R., Oertel, W. 1977. Amino acids—putative efferent transmitter in the cochlea. *Exp. Brain Res.* 30:145–48
41. Sand, O., Ozawa, S., Hagiwara, S. 1975. Electrical and mechanical stimulation of hair cells in the mudpuppy. *J. Comp. Physiol.* 102:13–26
42. Norris, C. H., Guth, P. S., Hastings, R. C. 1976. The infusion of picrotoxin, bicuculline, aminooxyacetic acid, and several putative transmitters on afferent transmission. *Fed. Proc.* 35:621
43. Klinke, R., Oertel, W. 1977. Evidence that GABA is not the afferent transmitter in the cochlea. *Exp. Brain Res.* 28:311–14
44. Felix, D., Ehrensberger, K. 1977. The action of GABA and acetylcholine in the labyrinth of the cat. *Inner Ear Biol.* 68:147–54
45. Bobbin, R. P., Gonzalez, G., Guth, P. S. 1969. Effects of aminooxyacetic acid on cochlear potentials and the Preyer reflex. *Nature* 223:70–71
46. Bobbin, R. P., Gondra, M. 1973. Effects of intravenous AOAA on guinea pig cochlear potentials. *Neuropharmacology* 12:1005–07
47. Monaghan, P., Osborne, M. P. 1976. Destruction of afferent nerve terminals in the inner ear of frog by aminooxyacetic acid. *Experientia* 32:1545–47
48. Desmedt, J. F., Monaco, P. 1962. The pharmacology of a centrifugal inhibitory pathway in the acoustic system. *Proc. Int. Pharmacol. Congr., 1st Stockholm, 1962,* 8:183–88
49. Guth, P., Sewell, W. F., Tachibana, M. 1981. The pharmacology of the cochlear afferents and cochlear nucleus. In *The Pharmacology of Hearing,* ed. R. D. Brown, pp. 99–136. New York: Wiley.
50. Thornhill, R. A. 1972. The effect of catecholamine precursors and related drugs on the morphology of synaptic bars in the vestibular epithelium of the frog. *Comp. Gen. Pharmacol.* 3:85–97
51. Densert, O. 1974. Adrenergic innervation in the rabbit cochlea. *Acta Oto-Laryngol.* 78:345–56
52. Fex, J., Fuxe, K., Lennerstrand, G. 1965. Absence of monoamines in olivocochlear fibers in the cat. *Acta Physiol. Scand.* 64:259–62
53. Klinke, R., Evans, E. F. 1977. Evidence that catecholamines are not the afferent transmitter in the cochlea. *Exp. Brain Res.* 28:315–24
54. Comis, S. D., Leng, G. 1979. Action of putative neurotransmitters in the guinea pig cochlea. *Exp. Brain Res.* 36:119–28
55. Klinke, R., Oertel, W. 1977. Evidence that 5-Ht is not the afferent transmitter in the cochlea. *Exp. Brain Res.* 30: 141–43
56. Douglas, W. W. 1975. Histamines and antihistamines. 5-HT and antagonists. In *The Pharmacological Basis of Therapeutics,* ed. L. F. Goodman, L. Gilman, pp. 609–46. New York: MacMillan. 1843 pp.
57. Stone, C. A., Wenger, H. C., Ludden, C. T., Stavorski, J. M., Ross, C. A. 1961. Antiserotonin-antihistaminic

properties of cyproheptadine. *J. Pharmacol. Exp. Ther.* 131:13–84
58. Aghajanian, G. K. 1976. LSD and 2-bromo-LSD: Comparison of effects on serotonergic neurons and on neurons in the serotonin projection areas: The ventral lateral geniculate and amygdala. *Neuropharmacology* 15:521–28
59. diCarlo, V. 1961. Ricerche sul meccanismo di azione degli anestetici locali. *Arch. Ital. Sci. Farmacol.* 11:3–12
60. Fex, J. 1973. Neuropharmacology and potentials of the inner ear. In *Basic Mechanics of Hearing,* ed. A. Moller, pp. 377–421. New York: Academic. 941 pp.
61. Klinke, R., Galley, N. 1974. Efferent innervation of vestibular and auditory receptors. *Physiol. Rev.* 51:316–57
62. Guth, P. S., Norris, C. H., Bobbin, R. P. 1976. The pharmacology of transmission in the peripheral auditory system. *Pharmacol. Rev.* 28:95–125
63. Gisselsson, L. 1950. Experimental investigations into the problem of humoral transmission in the cochlea. *Acta Oto-Laryngol.* 82:3–78 (Suppl.)
64. Vinnikov, Ya. A., Titova, L. K. 1964. *The Organ of Corti.* New York: Consultants Bureau. 253 pp.
65. Vinnikov, Ya. A. 1974. *Sensory Reception, Cytology, Molecular Mechanisms and Evolution.* Heidelberg: Springer Verlag. 336 pp.
66. Iurato, S., Luciano, L., Pannese, E., Reale, E. 1971. Histochemical localization of acetylcholinesterase (ACHE) activity in the inner ear. *Acta Oto-Laryngol.* Suppl. 279, pp. 6–50
67. Jasser, A., Guth, P. S. 1973. The synthesis of acetylcholine by olivocochlear bundle. *J. Neurochem.* 20:45–54
68. Godfrey, D. A., Krzanowski, J. J., Matschinsky, F. M. 1976. Activities of enzymes of the cholinergic system in the guinea pig cochlea. *J. Histochem. Cytochem.* 24:470–72
69. Bobbin, R. P., Konishi, T. 1974. Action of cholinergic and anticholinergic drugs at the COCB-hair cell junction. *Acta Oto-Laryngol.* 77:56–65
70. Robertson, D., Johnstone, B. M. 1978. Efferent transmitter substance in the mammalian cochlea single neuron support for acetylcholine. *Hearing Res.* 1:31–34
71. Fex, J. 1968. Efferent inhibition in the cochlea by the olivocochlear bundle. In *Hearing Mechanism in Vertebrates,* ed. A. S. DeReuck, J. Knight, pp. 169–86. Boston: Little, Brown. 320 pp.
72. Galley, N., Klinke, R., Oertel, W., Pause, M., Storch, W. H. 1973. The effect of intracochlearly administered acetylcholine blocking agents on the efferent synapses of the cochlea. *Brain Res.* 64:55–63
73. Konishi, T. 1972. Action of tubocurarine and atropine on the crossed olivocochlear bundle. *Acta Oto-Laryngol.* 74:252–64
74. Guth, P. S., Amaro, J. 1969. A possible cholinergic link in olivocochlear inhibition. *Neuropharmacology* 8:49–53
75. Steinbach, A. B., Bennett, M. V. L. 1971. Effects of divalent ions and drugs on synaptic transmission in a mormyrid fish. *J. Gen. Physiol.* 58:580–98
76. Norris, C. H., Guth, P. S. 1974. The release of acetylcholine by the crossed olivocochlear bundle. *Acta Oto-Laryngol.* 77:318–26
77. Bobbin, R. P., Thompson, M. H. 1978. Glutamate stimulates cochlear afferent nerve fibers. *Fed. Proc.* 37:2111
78. Usherwood, P. N. R. 1976. Excitatory amino acids. In *Chemical Transmission in the Mammalian Central Nervous System,* ed. C. N. Hockman, D. Biegler, pp. 83–158. Baltimore: Univ. Park Press. 442 pp.
79. Sewell, W. F., Norris, C. H., Tachibana, M., Guth, P. S. 1978. Detection of an auditory nerve activating substance. *Science* 202:910–12
79a. Gulley, R. L., Fex, J., Wenthold, R. J. 1979. Uptake of putative neurotransmitters in the organ of Corti. *Acta Oto-Laryngol.* 88:177–82
79b. Fex, J., Martin, M. R. 1980. Lack of effect of DL-α-aminoadipate, an excitatory amino acid antagonist, on cat auditory nerve responses to sound. *Neuropharmacology* 19:809–11
80. Spoendlin, H., Lichtensteiger, W. 1966. The adrenergic innervation of the labyrinth. *Acta Oto-Laryngol.* 61:423–24
81. Brown, R. D. 1972. Effects of PGE_1 on COCB stimulation in cats. *Arch. Int. Pharmacodyn Ther.* 198:372–76
82. Spoendlin, H., Lichtensteiger, W. 1965. Die adrenergische innervation des labyrinths. *Pract. Oto-Rhino-Laryngol.* 27:371–72
83. Spoendlin, H., Lichtensteiger, W. 1966. The adrenergic innervation of the labyrinth. *Acta Oto-Laryngol* 61:423–34
84. Spoendlin, H., Lichtensteiger, W. 1967. The sympathetic nerve supply to the inner ear. *Arch. Klin. Exp. Ohren- Nasen-Kehlkopfheilkd.* 189:346–59
85. Ross, M. D. 1971. Fluorescent and electron microscopic observations of the general visceral efferent innervation of

the inner ear. *Acta Oto-Laryngol.* Suppl. 286, pp. 3–18

86. Densert, O., Flock, A. 1974. An electron microscopic study of adrenergic innervation in the cochlea. *Acta Oto-Laryngol.* 77:185–97
87. Terayama, Y., Holtz, E., Beck, C. 1966. Adrenergic innervation of the cochlea. *Ann. Otol. Rhinol. Laryngol.* 75:69–86
88. Terayama, Y., Yamamoto, K., Sakamoto, J. 1968. Electron microscopic observations on the postganglionic sympathetic fibers in the guinea pig cochlea. *Ann. Otol. Rhinol. Laryngol.* 77:1152–70
89. Spoendlin, H. 1971. Degeneration behavior of the cochlear nerve. *Arch. Klin. Exp. Ohren- Nasen- Kehlokopfheilkd.* 200:245–91
90. Loewenstein, W. R. 1956. Modulation of cutaneous mechano-receptors by sympathetic stimulation. *J. Physiol.* 132:40–60
91. Santini, M. 1969. New fibers of sympathetic nature in the inner core region of pacinian corpuscles. *Brain Res.* 16:535

91a. Ross, M. D. 1973. Autonomic components of the VIII nerve. *Adv. Oto-Rhinol-Laryngol.* 20:316–36

92. Rasmussen, G. L. 1946. The olivary peduncle and other fiber projections of the superior olivary complex. *J. Comp. Neurol.* 84:141–219
93. Warr, W. B., Guinan, J. J. Jr. 1979. Efferent innervation of the organ of Corti: two separate systems. *Brain Res.* 173:152–55
94. Stopp, P. E., Comis, S. D. 1978. Afferent and efferent innervation of the guinea pig cochlea: A light microscopic and histochemical study. *Neuroscience* 3:1197–1206

94a. Stopp, P. E., Comis, S. D. 1979. Relationship of centrifugal fibers to supporting cells. *Arch. Otorhinolaryngol.* 224: 11–15

95. Wright, C. G., Preston, R. E. 1976. Efferent nerve fibers associated with the outermost supporting cells of the organ of Corti in the guinea pig. *Acta Oto-Laryngol.* 82:41–47
96. Galambos, R. 1956. Suppression of auditory nerve activity by stimulation of efferent fibers of the cochlea. *J. Neurophysiol.* 19:424–37
97. Fex, J. 1959. Augmentation of the cochlear microphonics by stimulation of efferent fibers to the cochlea. *Acta Oto-Laryngol.* 50:540–41
98. Fex, J. 1962. Auditory activity in centrifugal and centripetal cochlear fibers in cat. A study of a feedback system. *Acta Physiol. Scand.* 55: Suppl. 189, pp. 1–68
99. Dewson, J. H. III. 1968. Efferent olivocochlear bundle: Some relationships to stimulus discrimination in noise. *J. Neurophysiol.* 31:122–30
100. Trahiotis, C., Elliott, D. N. 1970. Behavioral investigation of some possible effects of sectioning the crossed olivocochlear bundle. *J. Acoust. Soc. Am.* 47:592–96
101. Borg, E. 1971. Efferent inhibition of afferent acoustic activity in the unanesthetized rabbit. *Exp. Neurol.* 31:301–12
102. Comis, S. D., Leng, G. 1979. Action of putative neurotransmitters in the guinea pig cochlea. *Exp. Brain Res.* 36:119–28
103. Iurato, S., Luciano, L., Pannese, E., Reale, E. 1971. Histochemical localization of acetylcholinesterase activity in the inner ear. *Acta Oto-Laryngol.* Suppl. 279, pp. 6–50
104. Fex, J., Adams, J. C. 1978. α-Bungarotoxin blocks reversibly cholinergic inhibition in the cochlea. *Brain Res.* 159:440–44
105. Fex, J., Altschuler, R. A. 1981. Enkephalin-like immunoreactivity of olivocochlear nerve fibers in cochlea of guinea pig and cat. *Proc. Natl. Acad. Sci. USA* 78:1255–59
106. Lim, D. G., Mogi, G., O'Dorisio, T. M., Cataland, S. 1981. Vasoactive intestinal peptide in perilymph. *Abstr. Assoc. Res. Otolaryngol.* p. 25
107. Wenthold, R. J., Gulley, R. L. 1977. Aspartic acid and glutamic acid levels in the cochlear nucleus after auditory nerve lesion. *Brain Res.* 138:111–23
108. Wenthold, R. J. 1978. Glutamic acid and aspartic acid in subdivisions of the cochlear nucleus after auditory nerve lesion. *Brain Res.* 143:544–48
109. Godfrey, D. A., Carter, J. A., Berger, S. J., Matschinsky, F. M. 1976. Levels of putative transmitter amino acids in the guinea pig cochlea. *J. Histochem. Cytochem.* 26:468–72
110. Godfrey, D. A., Carter, J. A., Berger, S. J., Lowry, O. H., Matschinsky, F. M. 1977. Quantitative histochemical mapping of candidate transmitter amino acids in cat cochlear nucleus. *J. Histochem. Cytochem.* 25:417–31
111. Godfrey, D. A., Carter, J. A., Lowry, O. H., Matschinsky, F. M. 1978. Distribution of gamma-aminobutyric acid, glycine, glutamate and aspartate in the cochlear nucleus of the rat. *J. Histochem. Cytochem.* 26:118–26

112. Bird, S. J., Gulley, R. L., Wenthold, R. J., Fex, J. 1978. Kainic acid injections result in degeneration of cochlear nucleus cells innervated by the auditory nerve. *Science* 202:1037–80
113. Caspary, D. M., Havey, D. C., Faingold, C. L. 1979. Effects of micro-iontophoretically applied glycine and GABA on neuronal response patterns in the cochlear nuclei. *Brain Res.* 172:179–85
113a. Zarbin, M. A., Wamsley, J. K., Kuhar, M. J. 1981. Glycine receptor: Light microscopic autoradiographic localization with ^{3}H-strychnine. *J. Neurosci.* 1: 532–47
114. Wenthold, R. J. 1979. Release of endogenous glutamic acid, aspartic acid, and GABA from cochlear nucleus slices. *Brain Res.* 162:338–43
115. Canzek, V., Reubi, J. C. 1980. The effect of cochlear nerve lesion on the release of glutamate, aspartate, and GABA from cat cochlear nucleus, in vitro. *Exp. Brain Res.* 38:437–441
116. Hansson, E., Jarlstedt, J., Sellstrom, A. 1980. Sound stimulated ^{14}C-glutamate release from the nucleus cochlearis. *Experienta* 36:576–77
117. Wenthold, R. J. 1980. Glutaminase and aspartate aminotransferase decrease in the cochlear nucleus after lesion of the auditory nerve. *Brain Res.* 190:293–97
118. Martin, M. R., Adams, J. C. 1979. Effects of DL-α-aminoadipate on synaptically and chemically evoked excitation of anteroventral cochlear nucleus neurons of the cat. *Neuroscience* 4:1097–1105
119. Tachibana, M., Kuriyama, K. 1974. Gamma-aminobutyric acid in the lower auditory pathway of the guinea pig. *Brain Res.* 69:370–74
120. Davies, W. E. 1975. The distribution of GABA transaminase-containing neurons in the cat cochlear nucleus. *Brain Res.* 83:27–33
121. Whitfield, I. C., Comis, S. D. 1966. The interaction of centrifugal and centripetal stimulation on neurones of the cochlear nucleus: final report, Part II. *AF EOAR* 63–115
122. Fex, J., Wenthold, R. J. 1976. Choline acetyltransferase, glutamate decarboxylase and tyrosine hydroxylase in the cochlea and cochlear nucleus of the guinea pig. *Brain Res.* 109:575–85
123. Davies, W. E. 1978. Gabanergic innervation of the mammalian cochlear nucleus. *Inner Ear Biol.* 68:155–63
124. Comis, S. D., Davies, W. E. 1969. Acetylcholine as a transmitter in the cat auditory system. *J. Neurochem.* 16: 423–29
125. Osen, K. K., Roth, K. 1969. Histochemical localization of cholinesterases in the cochlear nuclei of the cat, with notes on: the origin of acetylcholine-positive afferents and the superior olive. *Brain Res.* 16:165–82
126. Godfrey, D. A., Williams, A. D., Matschinsky, F. M. 1977. Quantitative histochemical mapping of enzymes of the cholinergic system in cat cochlear nucleus. *J. Histochem. Cytochem.* 25:397–416
127. Rasmussen, G. L. 1964. Anatomic relationships of the ascending and descending auditory systems. In *Neurological Aspects of Auditory and Vestibular Disorders,* ed. W. S. Fields, B. R. Alford, pp. 5–19. Chas C. Thomas: Springfield, Ill.
128. Comis, S. D., Guth, P. S. 1974. The release of acetylcholine from the cochlear nucleus upon stimulation of the crossed olivocochlear bundle. *Neuropharmacology* 13:633–41
128a. Godfrey, D. A., Matschinsky, F. M. 1981. Quantitative distribution of choline acetyltransferase and acetylcholinesterase activities in the rat cochlear nucleus. *J. Histochem. Cytochem.* 29:720–30
129. Comis, S. D., Whitfield, I. C. 1965. The effect of acetylcholine on neurones of the cochlear nucleus. *J. Physiol.* 183: 22–23
130. Hunt, S., Schmidt, J. 1978. Some observations on the binding patterns of α-bungarotoxin in the central nervous system of the rat. *Brain Res.* 157:213–32
130a. Wamsley, J. K., Lewis, M. S., Young, W. S. III, Kuhar, M. J. 1981. Autoradiographic localization of muscarinic cholinergic receptors in rat brainstem. *J. Neurosci.* 1:176–91
130b. Rotter, A., Birdsall, N. J. M., Field, P. M., Raisman, G. 1979. Muscarinic receptors in the central nervous system of the rat. II. Distribution of binding of (^{3}H) propylbenzilylcholine mustard in the midbrain and hindbrain. *Brain Res. Rev.* 1:167–83
131. Jones, S. W., Galasso, R. T., O'Brien, R. D. 1977. Nicotine and α-bungarotoxin binding to axonal and non-neural tissues. *J. Neurochem.* 29: 803–09
132. Pickles, J. O., Comis, S. D. 1976. Role of centrifugal pathways to cochlear nucleus in detection of signals in noise. *J. Neurophysiol.* 36:1131–37

133. Pickles, J. O. 1976. Role of centrifugal pathways to cochlear nucleus in determination of critical bandwidth. *J. Neurophysiol.* 39:394–400
134. Kromer, L. F., Moore, R. Y. 1976. Cochlear nucleus innervation by central norepinephrine neurons in the rat. *Brain Res.* 118:531–37
135. Swanson, L. W., Hartman, B. K. 1975. The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. *J. Comp. Neurol.* 163:467–506
135a. Versteeg, D. H. G., van der Gugten, J., deJong, W., Palkovits, M. 1976. Regional concentrations of noradrenaline and dopamine in rat brain. *Brain Res.* 113:563–74
135b. Chikamori, Y., Sasa, M., Fujimoto, S., Takaori, S., Matsuoka, I. 1980. Locus coeruleus-induced inhibition of dorsal cochlear nucleus neurons in comparison with lateral vestibular nucleus neurons. *Brain Res.* 194:53–63
136. Comis, S. D., Whitfield, I. C. 1968. Influence of centrifugal pathways on unit activity in the cochlear nucleus. *J. Neurophysiol.* 31:62–68
137. Pickles, J. O. 1976. The noradrenaline-containing innervation of the cochlear nucleus and the detection of signals in noise. *Brain Res.* 105:591–96
138. Fuxe, K. 1965. The distribution of monamine terminals in the central nervous system. *Acta Physiol. Scand.* 64(247):40–85
138a. Palacios, J. M., Wamsley, J. K., Kuhar, M. J. 1981. The distribution of histamine H_1-receptors in the rat brain: An autoradiographic study. *Neuroscience* 6:15–37
138b. Contreras, N. E. I. R., Bachelard, H. S. 1979. Some neurochemical studies on auditory regions of mouse brain. *Exp. Brain Res.* 36:573–84
139. Leeman, S. E., Mroz, E. D. 1974. Substance P. *Life Sci.* 15:2033–44
140. Ljungdahl, A., Hokfelt, T., Nilsson, G. 1978. Distribution of substance P-like immunoreactivity in the central nervous system of the rat. I. Cell bodies and nerve terminals. *Neuroscience* 3:861–943
140a. Uhl, G. R., Goodman, R. R., Snyder, S. H. 1979. Neurotensin-containing cell bodies, fibers and nerve terminals in the brain stem of the rat: Immunohistochemical mapping. *Brain Res.* 167: 77–91
141. Tachibana, M., Rothman, M. J., Guth, P. S. 1979. Somatostatin along the auditory pathway. *Hearing Res.* 1:379–82
142. Takatsuki, K., Shiosaka, S., Sakanaka, M., Inagaki, S., Senba, E., Takagi, H., Tohyama, M. 1981. Somatostatin in the auditory system of the rat. *Brain Res.* 213:211–16
142. Finley, J. C. W., Maderdrut, J. L., Petrusz, P. 1981. The immunocytochemical localization of enkephalin in the central nervous system of the rat. *J. Comp. Neurol.* 198:541–65
144. Herkenham, M., Pert, C. B. 1980. *In vitro* autoradiography of opiate receptors in rat brain suggests loci of opiatergic pathways. *Proc. Natl. Acad. Sci. USA* 77:5532–36
145. Hemsworth, B. A., Mitchell, J. F. 1968. The characteristics of acetylcholine release mechanisms in the auditory cortex. *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* 259:209–10
146. Fahrenkrug, J., Schaffalitzky de Muckadell, O. B. 1978. Distribution of vasoactive intestinal polypeptide (VIP) in the porcine central nervous system. *J. Neurochem.* 31:1445–51
147. Sasaki, H. E., Kadekaro, M., Sehle, J., Sokoloff, L. 1978. α- and β-adrenoceptor blockers have opposite effects on energy metabolism of the central auditory system. *Nature* 276:521–23
148. Fisher, S. K., Davies, W. E. 1976. GABA and its related enzymes in the lower auditory system of the guinea pig. *J. Neurochem.* 27:1145–55
149. Watanabe, T., Simada, S. 1973. Pharmacological properties of cat's collicular auditory neurons. *Jpn. J. Physiol.* 23:291–308
150. Adams, J. C., Wenthold, R. J. 1979. Distribution of putative amino acid transmitters, choline acetyltransferase and glutamate decarboxylase in the inferior colliculus. *Neuroscience* 4: 1947–51
151. Kobayashi, R. M., Palkovits, M., Kopin, I. J., Jacobowitz, D. M. 1974. Biochemical mapping of noradrenergic nerves arising from the rat locus coeruleus. *Brain Res.* 77:269–79
152. Dahlstrom, A., Fuxe, K. 1964. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brainstem neurons. *Acta Physiol. Scand.* 62(232):1–55
153. Fuxe, K. 1965. Evidence for the existence of monoamine neurons in the central nervous system. IV. Distribution of

monoamine nerve terminals in the central nervous system. *Acta Physiol. Scand.* 64:Suppl. 247, pp. 37–85

154. Masterton, R. B., Glendenning, K. K., Hutson, K. A. 1979. Preservation of trapezoid body fibers after biochemical ablation of superior olive with kainic acid. *Brain Res.* 173:156–59

155. Tebecis, A. K. 1974. *Transmitters and Identified Neurons in the Mammalian CNS,* pp. 123–35. Bristol: Scientechnia. 340 pp.

156. Oswald, R. E., Freeman, J. A. 1981. Alpha-bungarotoxin binding and central nervous system nicotinic acetylcholinic receptors. *Neuroscience* 6:1–14