Defant [plate 21 in (*7*)] and Leetmaa *et al.* [figure 1 in (*8*)]. Sverdrup *et al.* (*9*) and Worthington (*10*), on the other hand, require westward flow in the main thermocline of a few centimeters per second, corresponding to a zonal transit time of approximately 10 years.

Our knowledge of the decay of baroclinic eddies is also limited. It is known that newly formed Gulf Stream rings lose their anomalous water properties within 1 to 2 years after formation (*11*). Although their 100-km horizontal scale approximates that of the Meddy, they are considerably more energetic. If the rate of mixing within these baroclinic eddies is proportional to the radial shear, one can speculate that the containment time of the Meddy would be much greater than that of rings.

McCartney (*12*) has shown that barotropic vortices can propel themselves westward on a beta-plane (*13*). If this applies to baroclinic eddies as well, the Meddy would provide an efficient mechanism for large-scale preferentially zonal mixing. In this case, one may expect an upper bound for the intensity of a Meddy since both mixing and dissipation would be accelerated with increased baroclinicity.

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13. The beta-plane is a surface upon which latitudinal variations in the Coriolis parameter, f, are constant ($f = 2\omega \sin \theta$, where ω is the angular velocity of the earth's rotation and θ is the latitude).
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Kainic Acid Injections Result in Degeneration of Cochlear Nucleus Cells Innervated by the Auditory Nerve

Abstract. *When kainic acid, a putative neurotoxin for neurons with glutamatergic input, is injected into the brainstem, it produces a selective pattern of degeneration in the cochlear nucleus. The rate and extent of degeneration is correlated with the distribution of the primary auditory fibers. This evidence supports the hypothesis that glutamate is the neurotransmitter for primary auditory fibers.*

Evidence suggests that glutamate or aspartate, or both, may be neurotransmitters for the auditory nerve in the cochlear nucleus. The concentrations of both amino acids decrease in the cochlear nucleus (*1*) when primary auditory terminals degenerate, whereas several other amino acids (*1*) and the enzymes choline acetyltransferase, glutamate decarboxylase, and tyrosine hydroxylase (*2*) do not change. Aspartate has a distribution in the cochlear nucleus similar to that of the auditory nerve terminals (*3*), and the decreases in glutamate and aspartate after auditory nerve lesions are greatest in areas of the nucleus that contain the highest concentration of primary auditory terminals (*4*). Kainic acid, an analog and agonist of glutamic acid (*5*), causes selective degeneration when administered to the central nervous system in nanomole amounts (*6-8*). The neurotoxic effects of kainic acid may be due to its neuronal excitatory action (*9*), and present evidence suggests that neurons with receptors for glutamate may be especially susceptible to destruction by kainic acid (*6, 7*). To characterize further the synapses of the auditory nerve, we have studied the effects of kainic acid on neurons in the cochlear nucleus. Our results suggest that the destruction of neurons in the cochlear nucleus by kainic acid follows the distribution of auditory nerve synapses. This is additional evidence that auditory nerve synapses may use glutamate as a neurotransmitter.

Thirty male tricolor guinea pigs weighing 400 to 600 g were anesthetized with pentobarbital or methoxyflurane (or both) and stabilized in a stereotaxic apparatus. A hole was made in the skull over the right cerebellar hemisphere. With a micromanipulator, a 30-gauge needle attached to a 10-μl Hamilton syringe was positioned with the tip 4.5 mm anterior to the lambdoidal suture and 3.5 mm lateral to the sagittal suture and, at an angle of 18° to the vertical, lowered to a depth of 9 mm. These coordinates placed the tip of the needle in the middle cerebellar peduncle, 0.2 to 0.5 mm medial to the cochlear nucleus, at the level of the caudal anteroventral cochlear nucleus and the rostral posteroventral cochlear nucleus. The anteroventral cochlear nucleus and the posteroventral cochlear nucleus are equidistant to the injection site, and the dorsal cochlear nucleus is further by a factor of less than 1.5.

Phosphate-buffered saline containing 1.0, 0.5, 0.15, or 0.05 mg of kainic acid per milliliter, *p*H 7.4, was infused into the brainstem over 10 minutes. The volume infused was always 2 μl. Control injections consisted of α-methylaspartate (1 mg/ml in phosphate-buffered saline) and buffered saline alone. Animals were killed at 1, 3, 6, 12, 18, and 24 hours after injection by cardiac perfusion with 3 percent glutaraldehyde, 2 percent paraformaldehyde, and 0.005 percent $CaCl_2$ in 0.1*M* sodium cacodylate buffer. Slices of the brainstem containing the cochlear nuclei, both ipsilateral and contralateral to the injection site, were postfixed, dehydrated, and embedded by procedures described previously (*10*). Sections 1 to 2 μm thick from all regions of the cochlear nuclei were cut and examined with the light microscope. Two of the animals were injected with 2 μg of kainic acid as described above, and after 3 hours they were killed by perfusion with 10 percent formalin. The brainstem was removed and frozen serial sections, 20 μm thick, through the cochlear nucleus were cut in the parasagittal plane. These sections were stained with thionine.

The cochlear nucleus is divided into three anatomical divisions, the anteroventral cochlear nucleus, the posteroventral cochlear nucleus, and the dorsal cochlear nucleus (*11*). The anteroventral cochlear nucleus contains a homogeneous population of spherical cells at the rostral pole, dorsally (Fig. 1A); ventrally, smaller oval-shaped neurons occur among the spherical cells. A distinct layer of granule cells and other small neurons covers the anteroventral cochlear nucleus and extends over the posteroventral cochlear nucleus (Fig. 1A). The posteroventral cochlear nucleus and the dorsal cochlear nucleus contain populations of neurons heterogeneous in size and shape with the dorsal cochlear nucleus containing a distinguishable layer of fusiform cells.

One hour after injection of 2 μg of kainic acid, degenerating neurons were present in the ventral cochlear nucleus

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(Fig. 2A). Neuronal degeneration was greatest in the anteroventral cochlear nucleus with only scattered degeneration in the posteroventral cochlear nucleus. Some cells showed only early signs of karyolysis or vacuolization, while other cells were extremely swollen with only fragments of cytoplasm and nucleus remaining. However, most spherical cells in the anteroventral cochlear nucleus were normal.

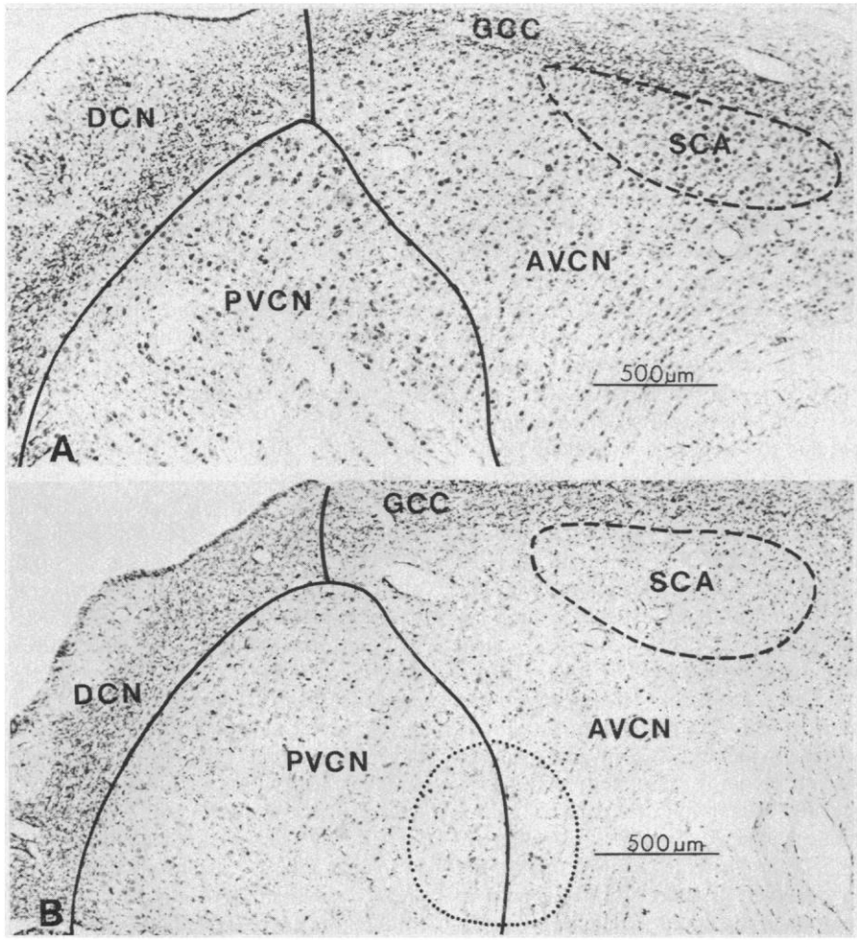

Fig. 1. (A) The cochlear nucleus from a normal guinea pig. (B) The cochlear nucleus from a guinea pig 3 hours after the injection of 2 μg of kainic acid. The injection site was located 180 μm medial to the area surrounded by dots. (Frozen 20-μm sections.) Major divisions of the cochlear nucleus, the anteroventral cochlear nucleus (*AVCN*), the posteroventral cochlear nucleus (*PVCN*), and the dorsal cochlear nucleus (*DCN*) are delimited by solid lines. The spherical cell areas (*SCA*) and granule cell cap (*GCC*) of the anteroventral cochlear nucleus are bounded by dashed lines.

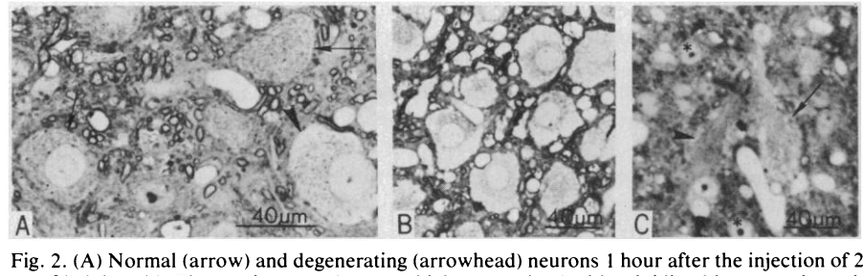

Fig. 2. (A) Normal (arrow) and degenerating (arrowhead) neurons 1 hour after the injection of 2 μg of kainic acid. The section (1 to 2 μm), which was stained with toluidine blue, was through the spherical cell area of the anteroventral cochlear nucleus. (B) Most spherical cells in the anteroventral cochlear nucleus are in advanced stages of degeneration 3 hours after the injection of 2 μg of kainic acid. This section (1 to 2 μm) is also through the spherical cell area of the anteroventral cochlear nucleus. (C) A fusiform neuron (arrow) with vacuolated cytoplasm and a fusiform neuron which appears normal (arrowhead) 24 hours after the injection of 2 μg of kainic acid. Granule cells appear normal (asterisks). Even at 24 hours after injection, the fusiform cells are less affected than are the spherical cells at 3 hours after injection. The section (1 to 2 μm) was through the dorsal cochlear nucleus.

Three hours after injection of 2 μg of kainic acid, almost all spherical cells in the anteroventral cochlear nucleus were in advanced stages of degeneration (Figs. 1B and 2B). Up to 12 hours after injection of 2 μg of kainic acid, there was a progressive loss of stellate cells in the anteroventral cochlear nucleus. The few remaining stellate cells were normal. There was no further degeneration of stellate cells at 18 and 24 hours, and granule cells did not degenerate up to 24 hours after injection. There was a progressive loss of neurons in the posteroventral cochlear nucleus from 3 to 24 hours after injection, with some neurons, both large and small, remaining after 24 hours. No degeneration was observed in the dorsal cochlear nucleus until 24 hours after injection, when scattered degenerating fusiform cells were present, while most of these cells were still normal (Fig. 2C).

The effects of decreasing doses of kainic acid were studied 3 hours after injection. Injection of 1 μg of kainic acid produced neuronal degeneration patterns similar to those seen with injection of 2 μg. Degeneration patterns after injection of 0.3 μg of kainic acid were similar to those after 2 μg of kainic acid, 1 hour after injection. Injections of 0.1 μg of kainic acid caused no degeneration after 3 hours.

Outside the cochlear nucleus, brainstem nuclei containing both large and small neurons, equidistant or closer to the injection sites than the cochlear nucleus, showed no evidence of degeneration. Beyond this distance, Purkinje cells of the cerebellum and neurons in the vestibular nuclei showed signs of degeneration 1 and 3 hours, respectively, after injection of 2 μg of kainic acid. Purkinje cells are believed to have glutamate receptors and have previously been shown to degenerate after injection of kainic acid into the cerebellum (*6*). Injections of α-methylaspartate, a nonneuroexcitatory analog of glutamate, or phosphate-buffered saline alone caused no neuronal degeneration up to 24 hours.

It has not yet been proved that glutamate is a neurotransmitter, and only indirect evidence suggests that kainic acid selectively destroys neurons that have glutamate receptors. While it has been suggested that kainic acid may not destroy neurons in the hippocampus that are purported to have glutamate receptors (*8*), in the cerebellum (*6*) and striatum (*7*) cells believed to have glutamate

receptors are selectively destroyed by kainic acid. Whether the neurotoxic effect of kainic acid is mediated through presynaptic elements or through direct action on postsynaptic receptors is not known. In transmission electron microscopic studies, primary auditory terminals are not altered up to 18 hours after injection of 2 μg of kainic acid (*12*).

Our data suggest that the neurotoxic effects of kainic acid are directly related to the amount of primary auditory innervation of the neurons in the cochlear nucleus. Spherical cells in the anteroventral cochlear nucleus, which degenerated early after kainic acid injection, receive large auditory nerve endings on their cell bodies (*10, 13*). Stellate cells, in the anteroventral and posteroventral cochlear nucleus, which degenerated more slowly after kainic acid injection, receive auditory nerve endings only on their dendrites (*10*). Fusiform cells were the only cells identified as degenerating in the dorsal cochlear nucleus after kainic acid injection. This degeneration did not occur until 24 hours after the injection. Correspondingly, the dorsal cochlear nucleus receives only a light innervation from the auditory nerve, mainly in the fusiform cell area, with auditory nerve terminals mostly on basal dendrites of fusiform cells (*13, 14*). Granule cells, on the surface of the anteroventral and posteroventral cochlear nucleus and also within the dorsal cochlear nucleus, receive no primary auditory innervation (*13*) and were unaffected by kainic acid.

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Feedback Inhibition of Brain Noradrenaline Neurons by Tricyclic Antidepressants: α-Receptor Mediation

Abstract. *The use of different receptor blocking agents and single-unit recording techniques indicates that feedback inhibition of brain noradrenaline neurons by tricyclic antidepressants is mediated by presynaptic α-receptors. After chronic imipramine treatment, noradrenaline neurons in the locus coeruleus of rat brain remained partly depressed, in agreement with clinical data. They were, however, resistant to further inhibition by imipramine or clonidine.*

Inhibition of reuptake at the nerve cell membrane of central monoamine neurons appears to be a major action of tricyclic antidepressant drugs (*1*). Secondary amines such as desipramine (DMI) are particularly potent on noradrenaline (NA) neurons, whereas tertiary amines such as imipramine (IMI) are more potent blockers of serotonin (5-hydroxytryptamine) (5-HT) uptake in vivo (*1*). The monomethylated antidepressants (such as DMI) preferentially reduce

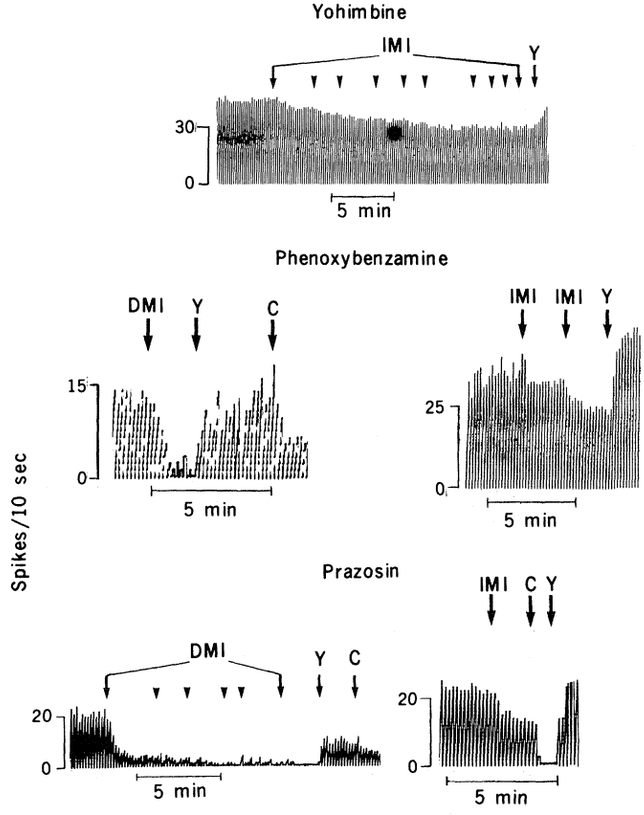

Fig. 1. Effect of various α-receptor blocking agents on the inhibition of locus coeruleus NA neurons by tricyclic antidepressants and clonidine. (Top) Treatment with yohimbine (*Y*), (10 mg/kg intraperitoneally), 30 minutes before recording almost completely blocked the inhibition by IMI (0.8 mg/kg intravenously, at arrows). Additional yohimbine (0.5 mg/kg intravenously) quickly reversed the weak inhibition ($n = 6$). (Middle) Treatment with phenoxybenzamine (10 mg/kg intraperitoneally) 30 minutes before recording did not block the inhibition by DMI (0.5 mg/kg intravenously) ($n = 4$) and only partially blocked that of IMI (0.8 mg/kg intravenously, at arrows) ($n = 3$). Both effects were rapidly reversed by yohimbine (0.5 mg/kg intravenously), after which clonidine (*C*) (20 μg/kg intravenously) only partially inhibited the firing rate of the unit. (Bottom) Treatment with prazosin (0.6 mg/kg intraperitoneally) 30 minutes before recording did not prevent the decrease in firing rate by DMI (0.20 mg/kg intravenously, at arrows) ($n = 4$), or by IMI (0.8 mg/kg intravenously) ($n = 3$) and clonidine (20 μg/kg intravenously), which completely silenced the cell. In contrast yohimbine (0.5 mg/kg intravenously) promptly restored the activity of the neuron.

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