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REVIEW ARTICLE

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The role of the inferior colliculus in a genetic model of audiogenic seizures

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Abstract Previous studies have shown the functional importance of the inferior colliculus (IC) for the propagation and initiation of audiogenic seizures in several models of epilepsy in rats. A review of the cell types and cytoarchitecture of the IC, including its three major subdivisions, is presented. Significant increases in GABA levels and the number of GABAergic neurons are found in the central nucleus of the IC (ICCN) of genetically epilepsy-prone rats (GEPR-9s) as compared to Sprague-Dawley rats that do not display audiogenic seizures. Two independent anatomical methods were used to determine the number of GABAergic neurons, immunocytochemistry and in situ hybridization. In both types of preparation, the labeled cells in the ICCN appeared to be of different sizes but the number of small cells with diameters less than 15 μm showed the greatest increase. Nissl-stained sections showed that the total number of neurons in the ICCN was increased in GEPR-9s and indicated that the increase in GABAergic neurons was not due to a change in the phenotype of collicular neurons from non-GABAergic to GABAergic. The number of small neurons in Nissl-stained sections of the ICCN was shown to correlate with seizure severity in the offspring of crosses made between Sprague-Dawley rats and GEPR-9s. Furthermore, the GEPR-3s that display moderate seizures showed a significant increase in the number of small neurons in the ICCN, and the magnitude of this increase was predicted from this correlation. Finally, the use of knife cuts through the midbrain indicated that the ICCN sends an important projection to the external nucleus and that this projection plays a vital role in the propagation of seizure activity from the site of seizure initiation in the ICCN. It remains to be resolved how the increase in small GABAergic neurons in the ICCN is responsible for the known pharmacological defects observed at GABAergic synapses.

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Introduction

The inferior colliculus (IC), so named for its position relative to the superior colliculus (SC), is a major relay nucleus in the midbrain for ascending auditory information en route to the ipsilateral medial geniculate body of the thalamus. Thus, it is virtually the exclusive recipient of fibers from the lateral lemniscus and receives input from both ears. Projection neurons in the IC send their axons rostrally into the brachium of the IC and terminate in the medial geniculate body. The IC plays a role in the ability to lateralize the side on which a sound originates. It is also involved in auditory reflexes. As will be discussed later in detail, the central nucleus of the IC (ICCN) is of particular interest because previous work has indicated a large increase in both the number of GABAergic neurons and the total neuronal number in a genetic model of epilepsy (Roberts et al. 1985b; Roberts and Ribak 1988). The IC is required for the expression of audiogenic seizures (Kesner 1966; Wada et al. 1970). IC neurons exhibit elevated thresholds to sound and a smaller degree of firing reduction during binaural inhibition in a model of epilepsy (Faingold et al. 1986b). This same epilepsy-prone animal model also shows an increase in afterdischarge-like responses similar to those observed in other types of epilepsies (Faingold et al. 1986b). Our laboratory has continued to investigate the role of the IC in this genetic model of epilepsy, and has obtained data to indicate the importance of this structure in the initiation and propagation of seizure activity.

Structure of the inferior colliculus

The IC of rats was elegantly described by Faye-Lund and Osen (1985). Utilizing Golgi, Nissl, and myelin staining techniques, they identified three substantial fiber tracts

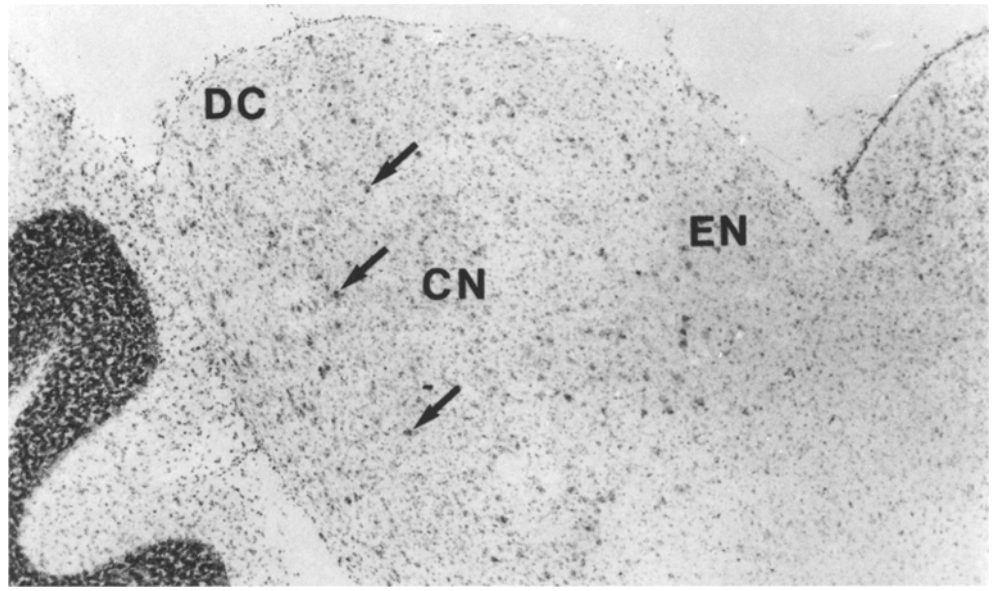

Fig. 1 Photomicrograph of the inferior colliculus (IC) from a GEPR-9 rat. In this Nissl-stained parasagittal section, many large cells show dense accumulations of silver grains *(arrows)* for GAD_{67} mRNA in the three subdivisions of the IC, the central nucleus (*CN*), external nucleus (*EN*) and the dorsal cortex (*DC*). ×75. Published with permission from Ribak et al. (1993)

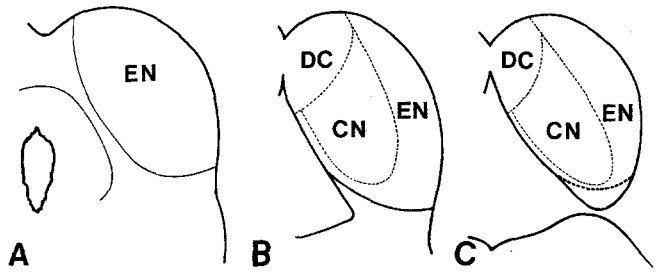

Fig. 2A–C Line drawings of coronal sections of the rat IC to show the three major subdivisions. **A** A rostral section where the only nucleus present is EN. **B** Section through the middle of the IC, displaying all three subdivisions. The CN is centrally located, the EN is now lying laterally and the DC is medial and dorsal. **C** A caudal section where all three subdivisions have a similar relationship. Modified from Saldaña and Merchán (1992)

and three main subdivisions of the IC. Briefly, the fiber tracts include the lateral lemniscus, the commissure of the IC and the brachium of the IC. The lateral lemniscus fiber tract enters the IC ventrally and the fibers course dorsally to form a myelin-rich area called the "lemniscal field." The commissure of the IC is most prominent in the rostral-most part of the IC and provides a conduit for communication between the two sides of the IC. It widens as it courses rostrally, and some of its fibers remain at the dorsal surface of the IC. The third fiber tract, the brachium of the IC, projects rostroventrally from the lateral region of the IC and courses through the external nucleus before reaching the brachium. As seen in the commissure of the IC, some fibers continue on the dorsal surface of the IC to form a myelinated, fibrous encapsulation of the IC.

It is generally agreed that three subdivisions exist in the IC of mammals (Fig. 1): the central nucleus (ICCN), external nucleus (EN), and the dorsal cortex (DC) (Cajal 1911; van Noort 1969; Geneic and Morest 1971; Rockel and Jones 1973a, b; FitzPatrick 1975; Ryugo and Killackey 1975; Harrison 1978; Willard and Ryugo 1983; Aitkin et al. 1984; Morest and Oliver 1984; Oliver and Morest 1984; Faye-Lund and Osen 1985). The ICCN forms a central core that is surrounded by the EN and DC (Fig. 2). In parasagittal sections the EN represents the ventral two-thirds of the IC, whereas the DC occupies the dorsal one-third of the IC (Fig. 1). In addition, the EN can be found at the ventral-lateral and ventral-rostral aspects of the IC. The DN is also located dorsomedial to the ICCN.

The ICCN contains principal neurons and multipolar (stellate) neurons (Geniec and Morest 1971; Rockel and Jones 1973b). A banding pattern can be found parallel to the principal neurons that display a disc-like shape with their dendritic arbors (Faye-Lund and Osen 1985). Three sizes of neurons have been described, large, medium and small. In the ICCN, there was little variation between these cell sizes. Bands of myelinated axons contributed to the lamination pattern in the ICCN (Faye-Lund and Osen 1985). The EN subdivision can be divided into three layers and is the only subdivision that has multipolar cells with prominent Nissl bodies. The DC is also described as a three-layered structure.

Afferents and efferents of the three regions of the inferior colliculus

The IC is the target of fibers from the lateral lemniscus, auditory cortex (via the brachium of the IC) and the brainstem auditory nuclei (Adams 1979; Schweizer 1981; Aitkin and Phillips 1984; Druga and Syka 1984a, b; Faye-Lund and Osen 1985; Coleman and Clerici 1987; González-Hernández et al. 1987). It also receives input to a lesser degree from the contralateral IC (Friauf and Kandler 1990; Saldaña and Merchán 1992). Some somatosensory structures also project to the IC (Aitkin et

al. 1978, 1981; Coleman and Clerici 1987), as do certain visual structures (Itaya and van Hoesen 1982; Paloff et al. 1985), the substantia nigra (Olazábal and Moore 1989), and the globus pallidus (Yasui et al. 1990a). Furthermore, the IC connections from the cochlear nucleus, superior olivary complexes and lateral lemniscus are all present at birth, suggesting that they develop prenatally (Friauf and Kandler 1990).

In addition to receiving afferents from other structures, the IC also displays intrinsic connections. The ICCN has been shown to project topographically to the contralateral and ipsilateral IC. Saldaña and Merchán (1992) found that a laminar axonal plexus connects each point of the ICCN with regions in each of the three subdivisions, both contralaterally and ipsilaterally. There are also some projections found from the ICCN to the ventromedial border of the IC. The density of the projecting fibers varies, the greater density being seen closer to the ventromedial border. It has been suggested that this finding implicates this area as the structure responsible for the processing of auditory information because it does not display the precise topographic orientation of other areas of the IC (Saldaña and Merchán 1992). A recent study from our laboratory showed that lesions in the coronal plane made just rostral to the ICCN disrupted some of these intrinsic IC connections, causing a cessation of seizure activity in a genetic model of epilepsy in rats. In contrast, lesions that severed the connection between the IC and the SC merely attenuated the seizure activity, perhaps due to intact commisural IC fibers that allowed for the propagation of seizure activity (Ribak et al. 1994).

Commisural connections facilitate communication between the two sides of the IC. These commisural projections express a reciprocal relationship with the contralateral IC (Adams 1980; Schweizer 1981; Zook and Casseday 1982; Druga and Syka 1984a, b; Coleman and Clerici 1987; Saldaña and Merchán 1992). *Phaseolus* agglutinin lectin injections made into the IC labeled homotopic sites in the contralateral IC (Saldaña and Merchán 1992). Furthermore, stimulation of the commissural pathway produced a short-latency monosynaptic inhibitory response followed by an excitatory response and a late polysynaptic inhibitory response (Smith 1992). The IC projects heavily to the contralateral DC in particular (Moore and Goldberg 1963; van Noort 1969; Rockel and Jones 1973a; Saldaña and Merchán 1992).

It is generally accepted that efferent fibers from all three subdivisions of the IC project mostly to the ipsilateral medial geniculate body via the brachium of the IC (Kudo and Niimi 1978) or to the contralateral IC via the intercollicular commissure as discussed above. Other efferent projections include that from DC and EN of the IC to the whole rostrocaudal extent of the subparafascicular thalamic nucleus (Yasui et al. 1990b; González-Hernández et al. 1991), and the deep layers of the ipsilateral SC (Edwards et al. 1979; LeDoux et al. 1985). There is also evidence that the IC projects to the cerebellum via the dorsolateral pontine nucleus (Carey and Webster 1971; Aitkin and Boyd 1975).

The GABAergic neurons of the inferior colliculus

Light microscopy

The GABAergic neurons of the ICCN (Figs. 3, 4) displayed a heterogeneous population of somata including several sizes and morphological traits. However, most of the glutamate decarboxylase (GAD)-positive cells were small and multipolar (Roberts et al. 1985b). Labeled multipolar neurons were found in all sizes, although small and medium were the most common (Roberts and Ribak 1987a). Dendritic staining of GAD-positive somata showed that some cells had dendrites oriented either across a lamina or within a lamina (Fig. 4). Small, medium and large multipolar neurons were seen in the ICCN. Other somata were bipolar or fusiform, but most of the GAD-positive somata were small multipolar cells. The dendrites of multipolar cells differed from those of bipolar and fusiform cells in that they radiated in all directions within and/or across several laminae. In contrast, the bipolar and fusiform cells had polarized dendrites that were oriented either across or within a lamina. Most GAD-positive neurons in the DC were small, oval or fusiform, with a few multipolar cells. The EN contained

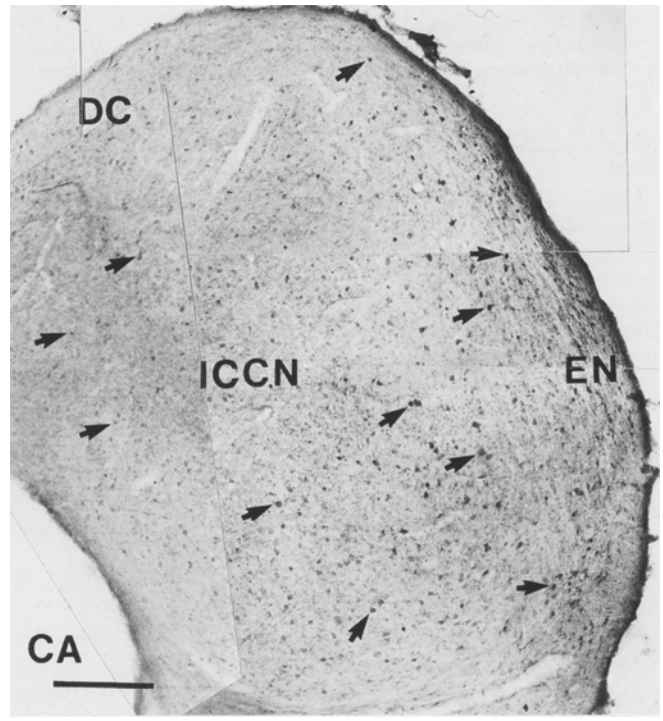

Fig. 3 Photomicrograph of the IC from a colchicine-treated gerbil to show GAD-positive neurons *(arrows)* located in all three major subdivisions (ICCN, EN and DC). The cerebral aqueduct (*CA*) is on the *left*. *Bar* 200 μm. Published with permission from Roberts and Ribak (1987a)

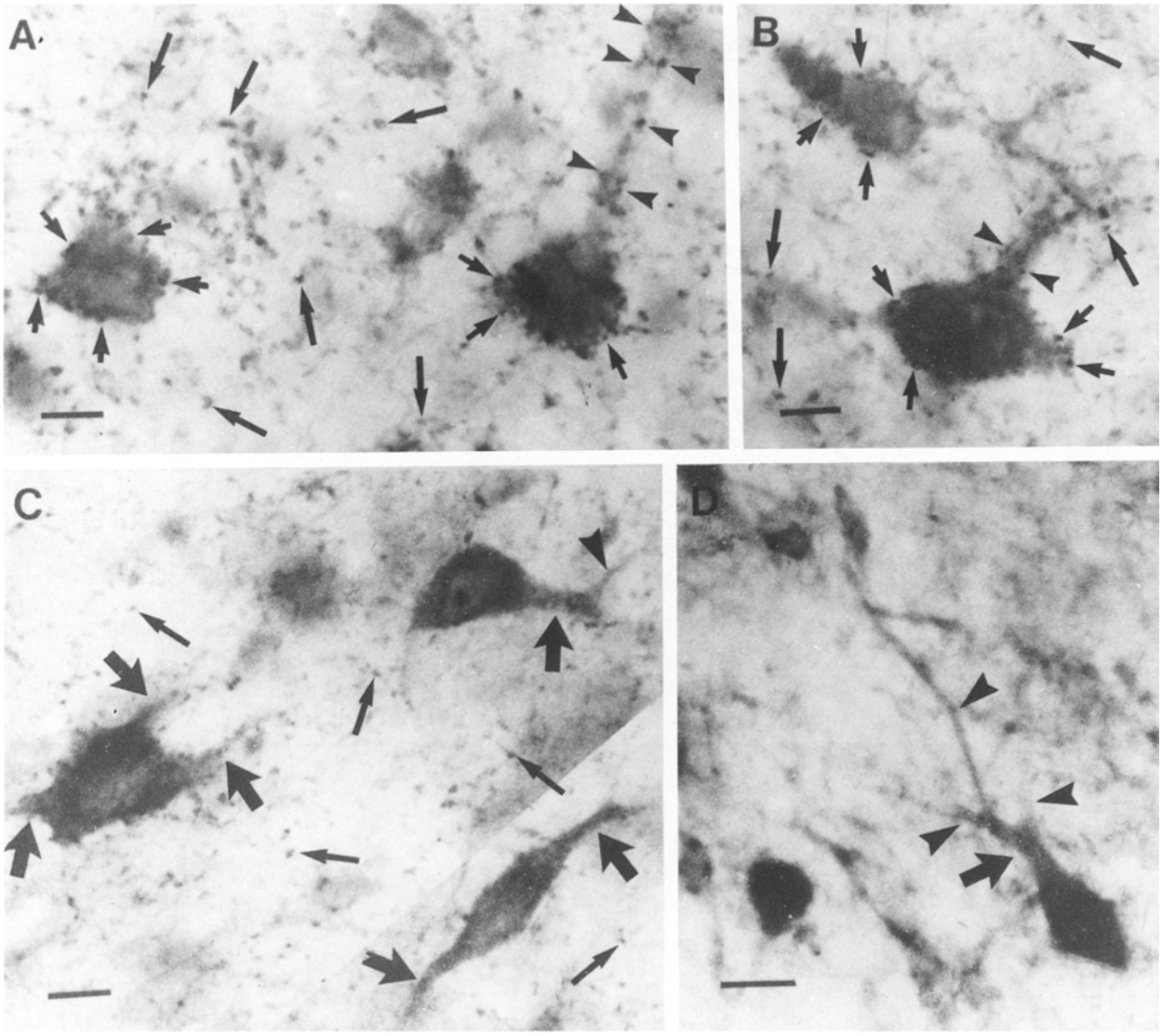

Fig. 4 Photomicrographs of the ICCN from nontreated (**A, B**) and colchicine-treated (**C, D**) gerbils. **A, B** GAD-positive puncta in the neuropil *(long, thin arrows),* adjacent to GAD-positive somata *(short arrows)* and adjacent to profiles of dendrites *(arrowheads).* The dendrites that emerge from the neuron on the *right* in **B** are oriented perpendicular to the laminae of the ICCN. **C, D** Multipolar and bipolar types of GAD-positive cell as well as puncta in the neuropil *(long, thin arrows).* Primary dendrites *(stout arrows)* and more distal dendrites *(arrowheads)* are stained. The two fusiform neurons have dendrites that run parallel to the laminae of the IC. *Bars* **A–C** 10 μm; **D** 15 μm. Published with permission from Roberts and Ribak (1987a)

medium-sized spindle or triangular-shaped GAD-positive cells, some of which were multipolar.

Numerous GAD-positive puncta (Fig. 4) were observed, and these correlate with axon terminals. GAD-positive puncta in the DC were not uniformly distributed and appeared in higher concentration in the superficial layers of the DC, whereas a moderate amount occurred in the deep layer (Roberts and Ribak 1987a). This finding parallels results from immunocytochemical studies in the guinea pig and mouse (Moore and Moore 1987).

Electron microscopy

GABAergic neurons in the ICCN of normal rats were examined at the electron microscopic level (Roberts and Ribak 1987b). Small, medium and large multipolar neurons as well as medium-sized fusiform neurons were found in this study. The multipolar neurons were all characterized by deeply infolded nuclei, many mitochondria, and both asymmetric and symmetric axosomatic synapses (Fig. 5). A concentration of axon terminals was found on the proximal dendrites of these GABAergic neurons, forming mostly asymmetric axodendritic synapses. The small GABAergic neurons (less than 15 μm in diameter) were multipolar. This type of neuron has infolded nuclear membranes, prominent nucleoli and a large nucleus to cytoplasm ratio. Two to five terminals contacting its soma in any section were typical. Most of these synapses were symmetric and contained flattened or pleomorphic vesicles. Dendrites of these small neurons were often traced for 30 μm from the soma, with a moderate number of axodendritic synapses, most of which were asymmetric.

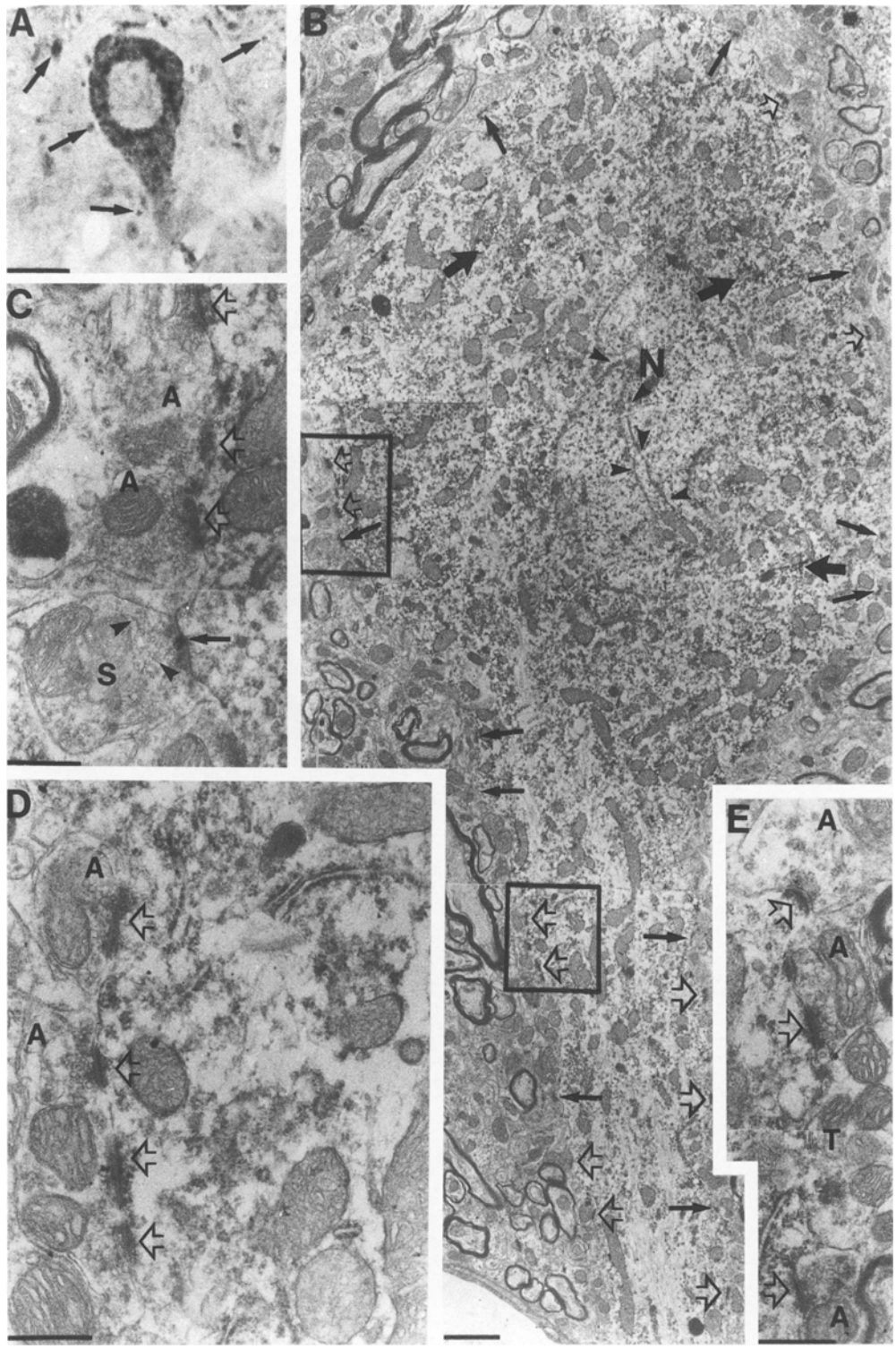

Fig. 5 **A** A photomicrograph of a semithin 2-μm section with a GAD-positive neuron that displays a fusiform soma. The nucleus is unstained whereas the cytoplasm displays immunoreaction product. GAD-positive puncta *(arrows)* appear in the adjacent neuropil. *Bar* 10 μm. **B** An electron micrograph of the same medium-sized neuron as in **A.** This neuron displays a centrally located, highly infolded *(arrowheads)* nucleus (*N*). Immunoreaction product *(stout arrows)* is present in the cytoplasm. Both asymmetric *(open arrows)* and symmetric *(small arrows)* axosomatic synapses are present. The *boxed area* of the soma is shown in **C** whereas the *boxed region* of the dendrite is enlarged in **D.** *Bar* 2 μm. **C** An enlargement of the somal surface. One axon terminal (*S*) with pleomorphic synaptic vesicles forms a symmetric synapse *(arrow),* whereas two adjacent axon terminals (*A*) form asymmetric synapses *(open arrows).* **D, E** Parts of the dendrite with asymmetric axodendritic synapses *(open arrows).* Bars in **C–E** 0.5 μm. Published with permission from Roberts and Ribak (1987b)

The medium-sized GABAergic neurons (15–20 μm in diameter) were either multipolar or fusiform and were richer in cytoplasm than the small cells. Most of these neurons had round somata and dendrites radiating from various poles of the soma. Like small neurons, medium-sized neurons had infolded nuclear membranes, abundant mitochondria, and a dense plexus which contacted its proximal dendrites. Medium-sized neurons had more axosomatic synapses in a single section than the small-sized neurons. Some medium-sized somata were fusiform with stout bipolar dendrites, centrally located nuclei, and abundant mitochondria. Their axosomatic synapses were similar to those of the round medium-sized somata. The proximal dendrites were contacted by a dense plexus of

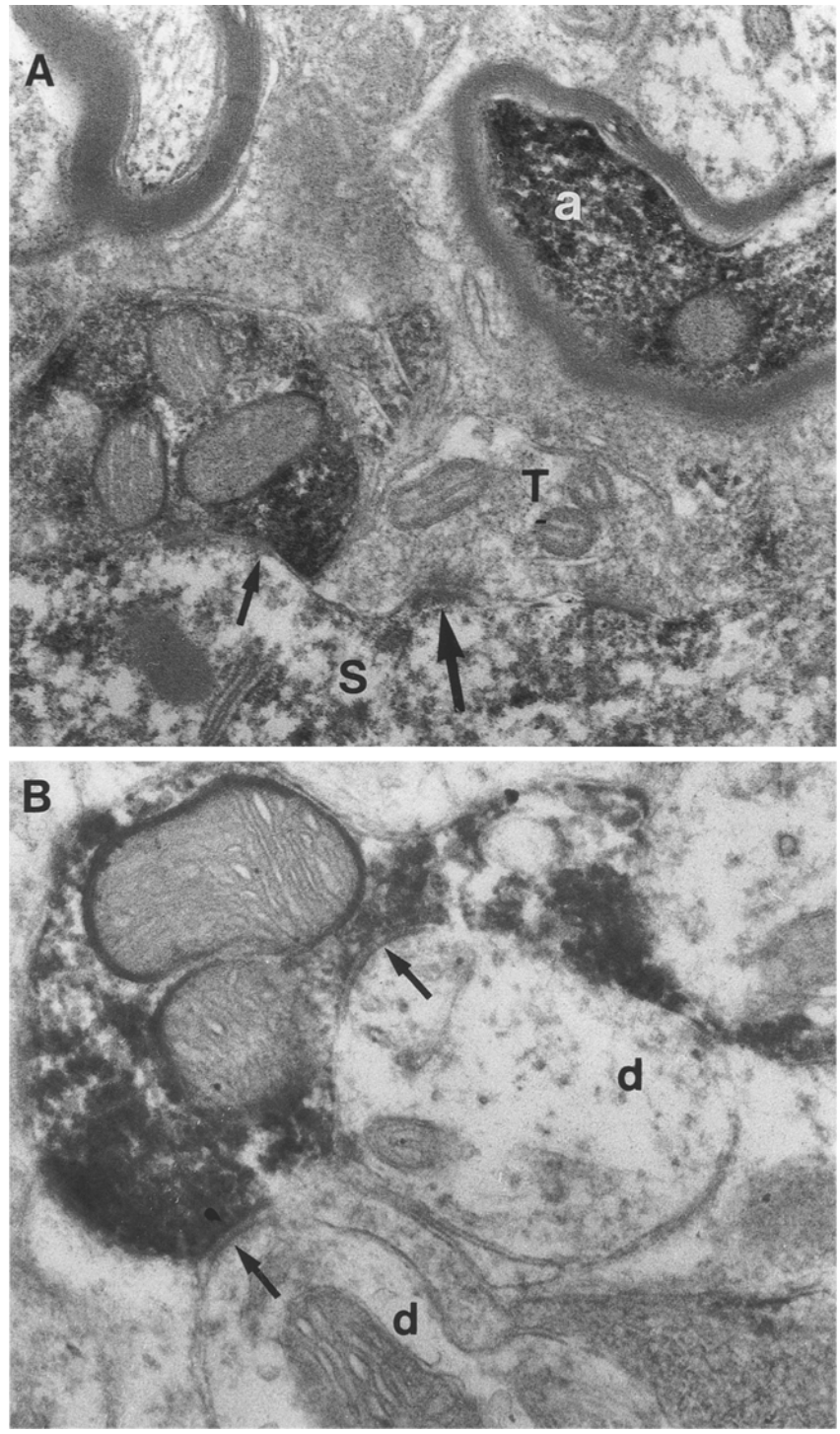

Fig. 6A, B Electron micrographs of GABAergic axon terminals in the ICCN. **A** A GAD-positive axon terminal that forms a symmetric synapse *(arrow)* with a GAD-positive soma (*S*). An adjacent non-immunoreactive axon terminal (*T*) forms an asymmetric synapse *(large arrow)*. A GAD-positive myelinated axon (*a*) is also shown. ×48,000. **B** A GABA-positive axon terminal that forms symmetric synapses *(arrows)* with two non-immunoreactive dendrites (*d*). ×60,000. Published with permission from Roberts and Ribak (1987b)

axon terminals that formed asymmetric synapses. Large GABAergic neurons (more than 25 μm in diameter) had highly infolded nuclei, abundant cytoplasm and a denser plexus of axon terminals forming axosomatic synapses than the other two cell types. Another group of terminals apposed the proximal dendrites where they formed asymmetric synapses. Large GABAergic neurons had round somata and dendrites that radiated from the cell body in many directions. These results suggest that of the six major cell types in the ICCN, four are GABAergic inhibitory neurons.

GAD-positive axon terminals contained pleomorphic synaptic vesicles and made symmetric synapses with somata and dendrites of both GAD-positive and GAD-negative profiles (Fig. 6). Axon terminals frequently formed synapses with more than one target in a given section. GAD-positive myelinated axons were also common in the ICCN.

The genetically epilepsy-prone rat model of genetic epilepsy

Genetically epilepsy-prone rats (GEPRs) exhibit convulsions when exposed to sound stimulus, and the seizures are scored on a 0–9 scale (0 being no seizure, and 9 being one fit of wild running and an accompanying tonic seizure, culminating in tonic hind limb extension). Young GEPR-9s exhibit running fits when 18 days old, in response to acoustic stimulus, and display their first audiogenic seizure (AGS) at 21 days of age. Seizure severity increases and latency decreases with age until, by day 60, the animal displays the tonic seizure of an adult GEPR-9 (Hjeresen et al. 1987; Ribak et al. 1988b; Reigel et al. 1989). No significant decrease in latency occurs, however, with senescence (Thompson et al. 1991). A rat strain that displays moderate seizures (running phase and forelimb/hindlimb clonus) and has an assigned seizure score of 3 (GEPR-3) is also used as an animal model for AGS (Jobe et al. 1986; Dailey et al. 1989; Mishra et al. 1989).

Results from lesion studies on GEPRs indicate that the primary neuronal pathways involved in AGS are subcortical, since partial or total ablation of the cortex fails to prevent seizures (Chocholova 1962). Bilateral lesions of the IC and brainstem reticular formation, however, did prevent seizures (Kesner 1966; Wada et al. 1970; Browning et al. 1985). Neurochemical studies have shown that there are numerous abnormalities in the IC of GEPRs, some of which will be discussed in detail later. GEPR-9s, from around the 2nd week of life until 1 year of age, are neurochemically similar to rats with hypothyroidism (Mills and Savage 1988). In addition to this abnormality, GEPR-9s also exhibit learning, memory, activity level, and behavioral deficits when exposed to frequent seizures while immature (Holmes et al. 1990). Seizure-prone animals were also examined for sex-specific differences, and it was found that female GEPR-9s show a higher frequency of seizures, greater seizure severity and a shorter latency than male GEPR-9s (Mishra et al. 1988). Studies of the offspring between GEPR-9s and normal Sprague-Dawley (SD) rats have revealed a ratio of seizure-prone to seizure-resistant offspring that is always greater than 3:1. This finding and others indicated that AGS susceptibility in GEPRs is an autosomal dominant trait (Ribak et al. 1988b).

Several ultrastructural abnormalities were observed in the IC of GEPR-9s. These included the presence of dendrites that were nearly devoid of organelles, hypertrophy of glial processes and terminals containing swollen or few vesicles (Roberts and Ribak 1988). The IC of GEPR-9s also displayed an abundance of extra membranes, whorl bodies and multivesicular bodies within somata, dendrites and axons. Both symmetric and asymmetric axosomatic synapses in the IC of GEPRs and SD rats were analyzed, and it was found that the number of these synapses for each cell type did not vary significantly (Roberts and Ribak 1988).

GEPRs display many anatomical and neurological abnormalities. One anatomical example is that of the cochlear morphology. Penny et al. (1983) conducted an electron microscopic analysis of the organ of Corti of GEPR-3s. Many abnormalities were found. Some animals displayed stereocilia aberrations of the hair cells, some were missing hairs in some regions of the cochlear turns, and the "headplate" of the organ of Corti showed several abnormalities. These cochlear aberrations may also con-

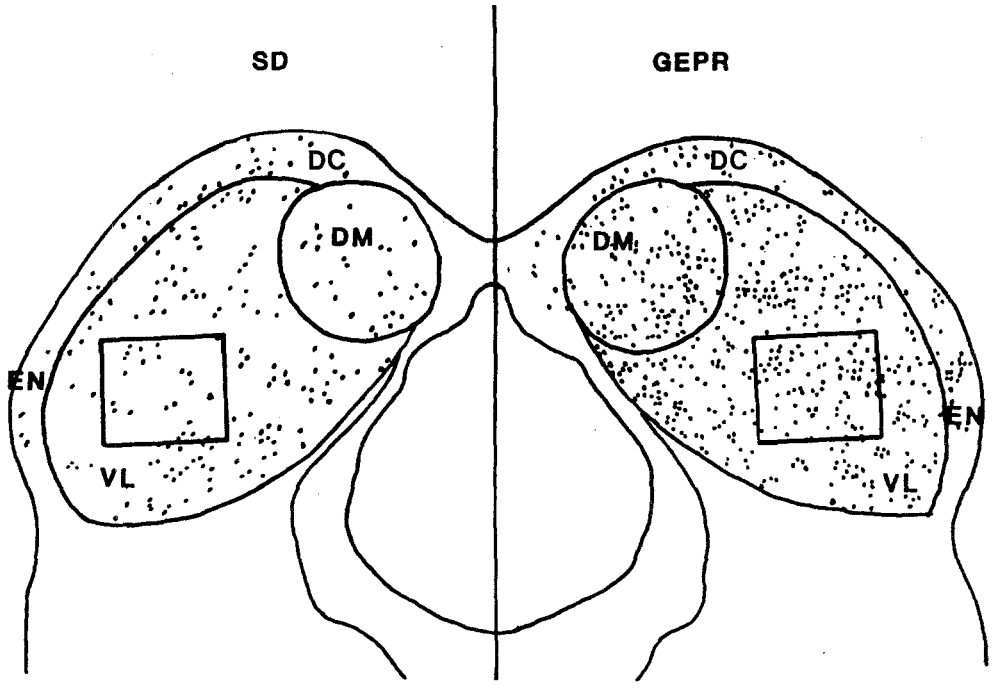

Fig. 7 Line drawing of a coronal section through the middle region of the rostrocaudal extent of the IC. The EN and DC are shown arranged as in Fig. 2B. The ICCN is divided into ventrolateral (*VL*) and dorsomedial (*DM*) parts. *Dots* represent GAD-positive somata counted from one representative section in the GEPR-9 and SD rat, respectively. Note the increased number of GABAergic neurons in the GEPR-9. Published with permission from Roberts et al. (1985b)

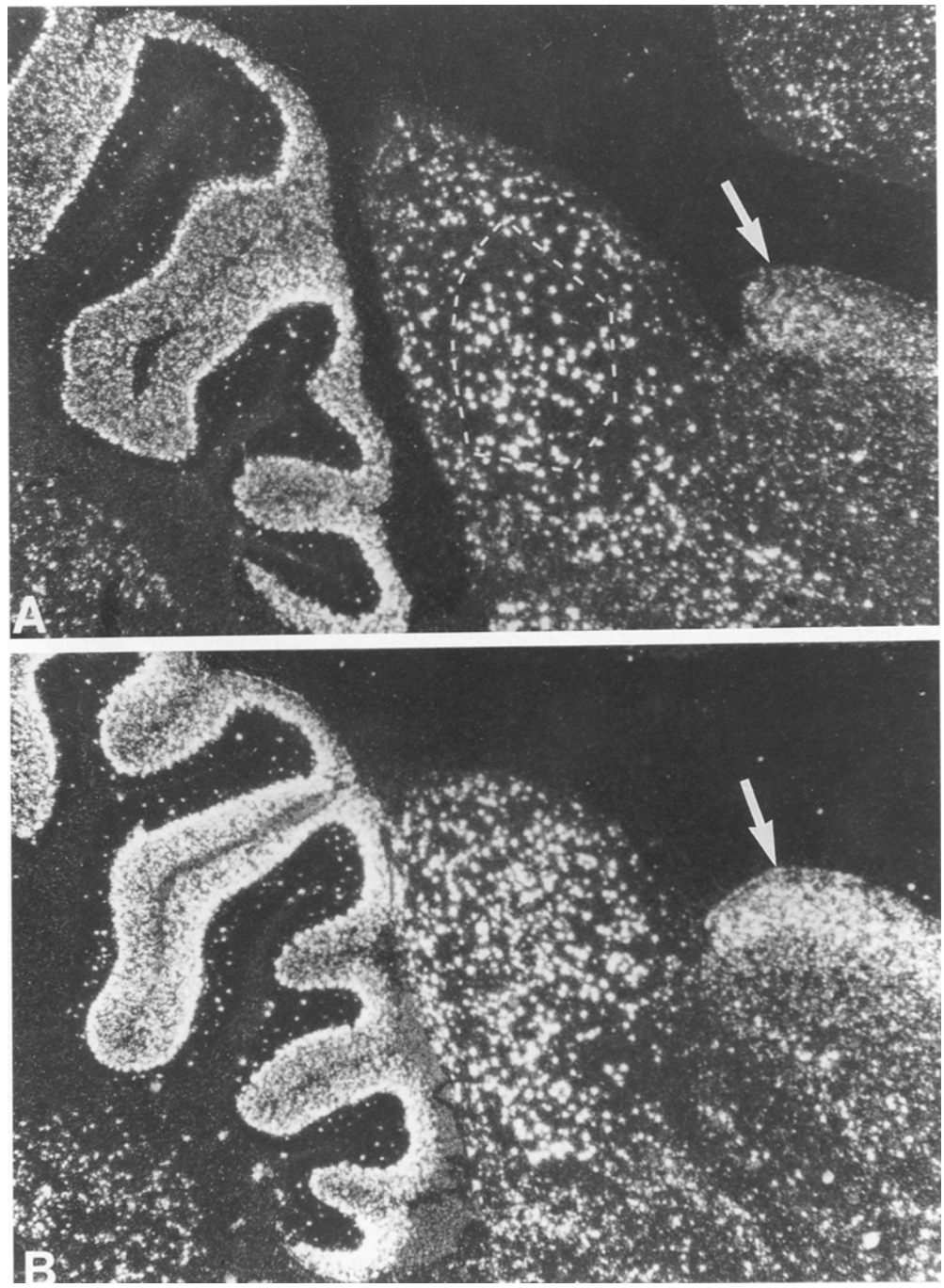

Fig. 8 Dark-field photomicrographs of the IC to show the GAD mRNA-labeled neurons in a SD rat (**A**) and GEPR-9 (**B**). Note that the number of labeled neurons in the IC from the GEPR-9 is greater than that of the SD rat. The boundary of the ICCN is indicated by a *white broken line* in **A.** The SC *(arrow)* shows an increase in the density of labeling in the GEPR-9 but not in the number of labeled cells. ×50. Published with permission from Ribak et al. (1993)

tribute to seizure susceptibility and intensity. Similarly, when the cochlea is damaged artificially in rats, AGS susceptibility can be induced (Faingold et al. 1990). Not only are GEPRs sensitive to acoustic stimulus, but they are also more likely to exhibit hyperthermic, hyperbaric, convulsant drug, kindling and spontaneous seizure activity than normal animals (Faingold and Naritoku 1992).

Studies have shown that the effect of exogenous application of the neurotransmitter GABA is abnormal in the IC (Faingold et al. 1986a). Infusion of GABA agonists into the IC attenuates seizure activity, whereas GABA antagonist infusion causes seizure activity (Duplisse 1976; Millan et al. 1986). Baclofen and gabaculine have both been shown to affect AGS in GEPR-9s. Baclofen, a GABA-B receptor agonist, protects against AGS. Gabaculine, a GABA transaminase inhibitor acts by preventing the breakdown of endogenous GABA, thereby raising GABA levels in the IC and blocking AGS activity (Faingold et al. 1994a). In another recent study, Faingold et al. (1994b) demonstrated that the anticonvulsant tiagabine, which blocks the uptake of GABA, inhibits AGS and reduces neuronal firing in the IC of GEPR-9s. Together, these findings emphasize the importance of GABA-mediated inhibition in the IC.

Increased numbers of GABAergic and total neurons in the inferior colliculus of GEPRs

Studies of GABAergic neurons

Using GAD immunocytochemistry, the distribution of GAD-positive neurons was studied in all three subdivisions of the IC of GEPR-9s (Roberts et al. 1985b). We found that the sizes and shapes of GAD-positive cells were similar to those observed in SD rats. Thus, we found small, medium and large neurons in GEPR-9s. However, a dramatic increase in the number of GAD-positive neurons was found in the IC of GEPR-9s as compared to that of SD rats (Fig. 7). This increase was most prominent in the middle of the rostrocaudal extent of the IC where the ICCN is most prominent and was largely due to a selective increase in small (200%) and medium (90%) GAD-positive cells. The number of GAD-positive large cells was similar in the two groups of animals. Statistically significant increases were also observed in the two other subdivisions. Thus, there were more GAD-positive cells present in the GEPR-9s in all subdivisions of the IC: ICCN, DC and EN.

Recently, our laboratory confirmed these immunocytochemical data using in situ hybridization and emulsion autoradiographic techniques (Ribak et al. 1993). We found higher numbers of neurons in the ICCN containing the 67-kDa form of mRNA in GEPR-9s than in normal SD rats (Fig. 8). This is the type of mRNA that codes for the GABA-synthesizing enzyme, GAD. The EN of the IC was also found to contain greater numbers of GAD_{67} cRNA-labeled neurons. These data are consistent with the immunocytochemical data. As expected, no differences were found in the frontal cortex, since this region is not involved in AGS activity in this genetic model of epilepsy. Some areas, such as the superficial layers of the SC, showed a greater density of autoradiographic grains in the GEPR-9 than in the SD rat. This density, however, did not appear to be associated with an increase in the number of labeled neurons (Ribak et al. 1993).

Neuron numbers obtained from Nissl-stained preparations of the inferior colliculus

The Nissl preparations of the IC of SD rats were similar to those described by Faye-Lund and Osen (1985). Thus, small, medium and large cell bodies were observed. They were homogeneously displayed in the ICCN. In contrast, the ICCN of GEPR-9s showed many more cell bodies, and these often formed clusters of three to five cells apposed to each other. Counts were made of the total number of Nissl-stained cells in the ICCN, and in addition, the three different sizes of ICCN neurons were separately counted (Roberts et al. 1985b).

The total number of neurons in the IC as determined by Nissl analysis of 10-μm-thick sections, was greater in the GEPR than in the SD rat (Fig. 9). Small neurons displayed the largest increase at 100%, followed by a 30% increase in the number of medium-sized neurons. This increase was found throughout the rostrocaudal extent of the ICCN.

It is interesting to note that the proportion of GAD-positive neurons to total neurons was found to be greater in the GEPR-9 than in the SD rat. Approximately 25% of the total number of small neurons in the SD rat are GAD-positive, compared to 36% for the GEPR-9. This pattern also occurred in the proportion of GAD-positive medium-sized neurons, with about 25% in the SD and about 30% in the GEPR-9 (Roberts et al. 1985b). This Nissl analysis of IC neurons indicated that the increase was not due to a change in the phenotype of collicular neurons from non-GABAergic to GABAergic. Also, this increase in total neuron number was present in young offspring of GEPR-9s (Roberts et al. 1985a).

Another study confirmed the increase in the numbers of neurons in the ICCN of the GEPR-9 (Roberts and Ribak 1988). This study of 2-μm semi-thin sections once again showed greater numbers of neurons in the ICCN of the GEPR-9 than in the SD rat. The abundant neurons of GEPR-9s were often clustered in groups of three to five, consisting mostly of small neurons. This observation was confirmed in electron microscopic preparations (Fig. 10). When these neurons were counted, it was found that both small (70%) and medium (30%) neurons in the ICCN of GEPR-9s were significantly more numerous than those in SD rats. Furthermore, many of the small neurons in the ICCN of the GEPR-9 were smaller than those in the SD rats (Roberts and Ribak 1988).

Not only do GEPR-9s show an increase in small neuron number in the ICCN, but this increase correlates with the seizure severity in offspring of GEPR-9s and SD rats (Ribak et al. 1988b). In comparing the audiogenic response score of GEPR-9s, SD rats, and the offspring of GEPR-9 X SD rat crosses, a significant positive correlation was established between the number of small neurons in the ICCN and the audiogenic response score (Ribak et al. 1988b). A nearly linear relationship (r=0.91) was found between the audiogenic response score and the number of small neurons (Fig. 11). The increase in neuron number is present in the ICCN of the offspring with seizures, but not in the progeny that did not display audiogenic seizures (Ribak et al. 1988b).

Studies of GEPR-3s

To determine the predictive value of the correlation between the audiogenic response score and the number of small neurons, the ICCN of GEPR-3s was analyzed. Recently, we completed an analysis of the brains of GEPR-3s for total neurons and GAD-positive neurons. The average number of small neurons in the ICCN of GEPR-3s was 29.50±2.17 cells per unit area. This value was significantly greater than that of SD rats and was similar to the value predicted by the linear relationship shown in Fig. 11. There seemed to be more GAD-positive cells in

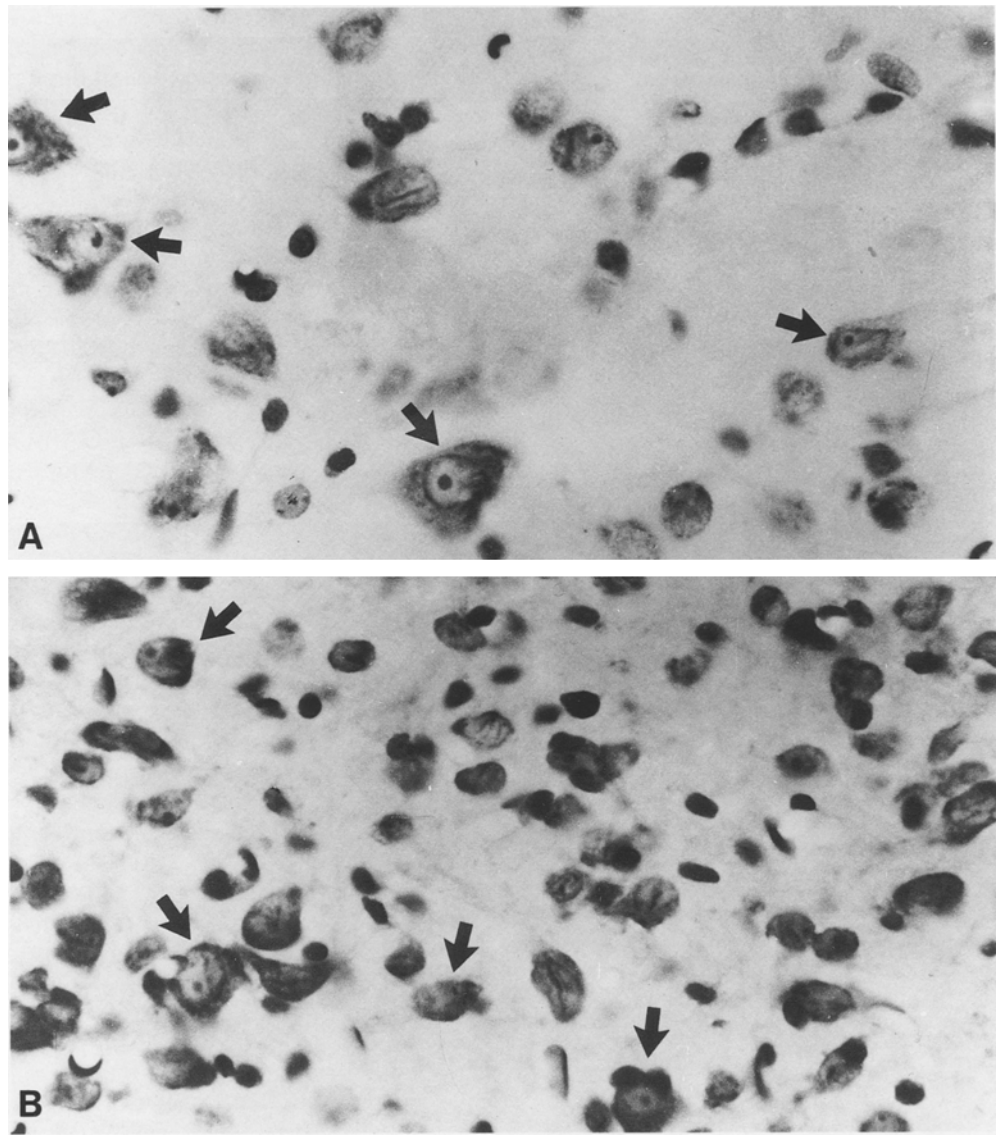

Fig. 9 Nissl preparations of neurons *(arrows)* and glia in the ICCN of a SD rat (**A**) and a GEPR-9 (**B**). The GEPR-9 displays a greater number of neuronal somata than the SD rat. ×. Published with permission from Roberts et al. (1985b)

the GEPR-3s than in normal SD rats, but the difference was not statistically significant.

Other neurotransmitter systems in GEPRs

Analysis of the amino acid neurotransmitters in the ICCN revealed a significant increase in GABA, glutamate and taurine levels (Ribak et al. 1988a). The increase in total GABA from the core of the IC (mainly ICCN tissue) is consistent with the findings of increased numbers of both GAD-positive and GAD mRNA-labeled neurons in the ICCN (see above).

Other studies of the GEPR-9 brain have demonstrated abnormalities in the noradrenergic and serotoninergic systems. A reciprocal relationship exists between these two systems and seizure susceptibility. Thus, a high correlation exists between the effectiveness of the noradrenergic and serotoninergic systems and the severity of the AGS (Jobe et al. 1986). Bilateral injection of norepinephrine, phenylephrine, clonidine or isoproterenol has no effect on AGS, whereas muscimol, a GABA agonist, ablates the tonic and clonic parts of the AGS when injected into the IC (Browning et al. 1989a). This shows that enhancement of GABAergic neurotransmission in the IC can diminish AGS activity, but enhancement of the noradrenergic system has an insignificant effect (Browning et al. 1989a). Dailey et al. (1991a, b) found that GEPR-3s and -9s display abnormal concentrations of norepinephrine in the spinal cord, midbrain (including the IC), hypothalamus, amygdala, occipital, parietal and frontal cortices, and olfactory septum suggesting that they may play a role in seizure susceptibility. The neurotransmitters norepinephrine and serotonin are also shown to be abnormal in the GEPR-9 (Jobe et al. 1973a, b; 1981, 1982; Laird 1974; Laird et al. 1974, 1984; Jobe and Brown 1980; Jobe and Laird 1981). Norepinephrine is one of the first neurotransmitter systems to develop,

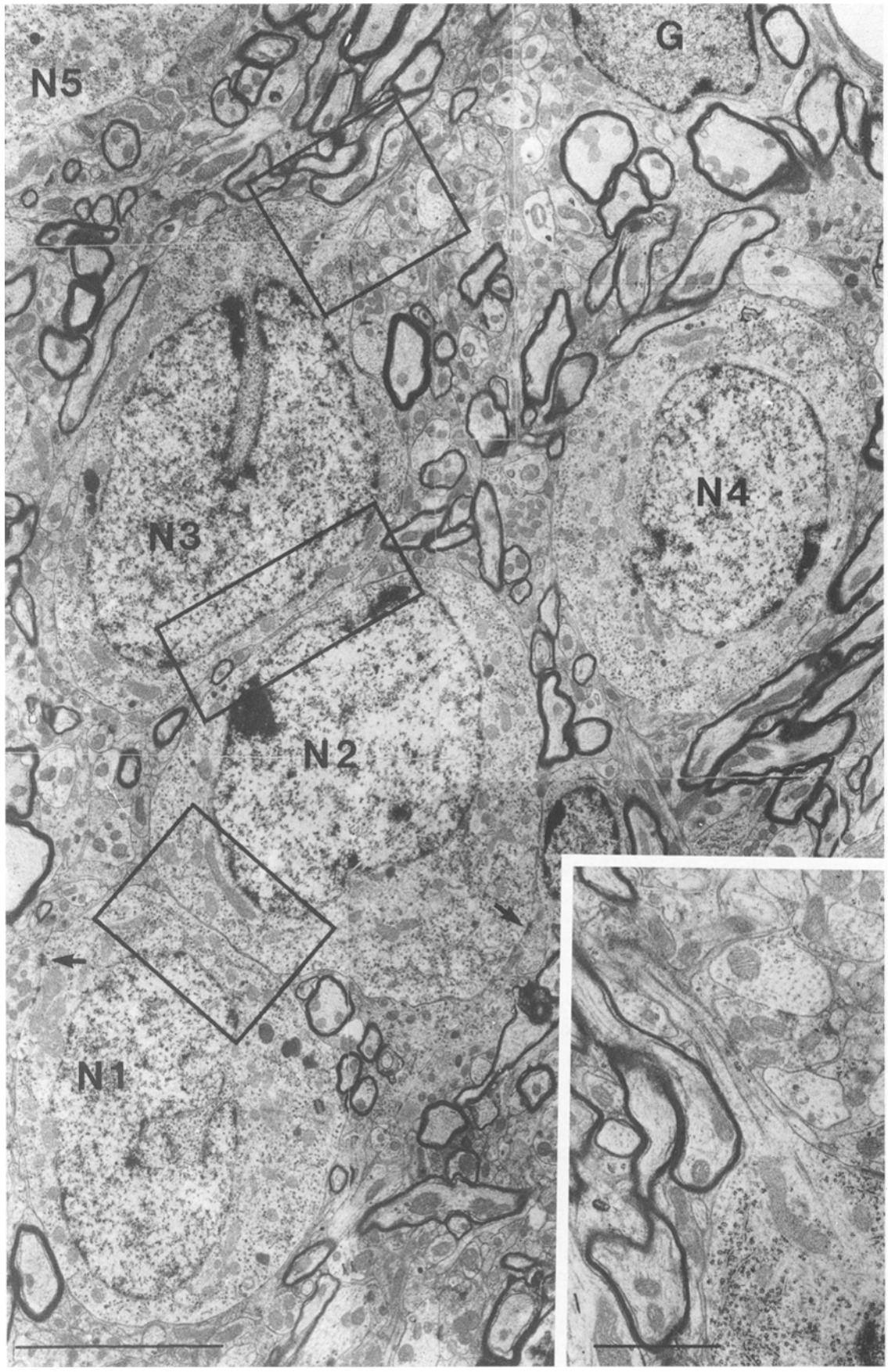

Fig. 10 Electron micrograph of the ICCN of a GEPR-9 to show a cluster of neuronal somata (*N1-4*). Neurons N1 and N2 are separated by a thin glial slip, whereas neurons N2 and N3 are separated by a thin margin of neuropil. An axon initial segment emerges from N3 and the *boxed area* of this region is shown at higher magnification in the *inset*. *Arrows* represent synapses, *G* indicates glia. *Bars:* 5.0 μm; inset 1.0 μm. Published with permission from Roberts and Ribak (1988)

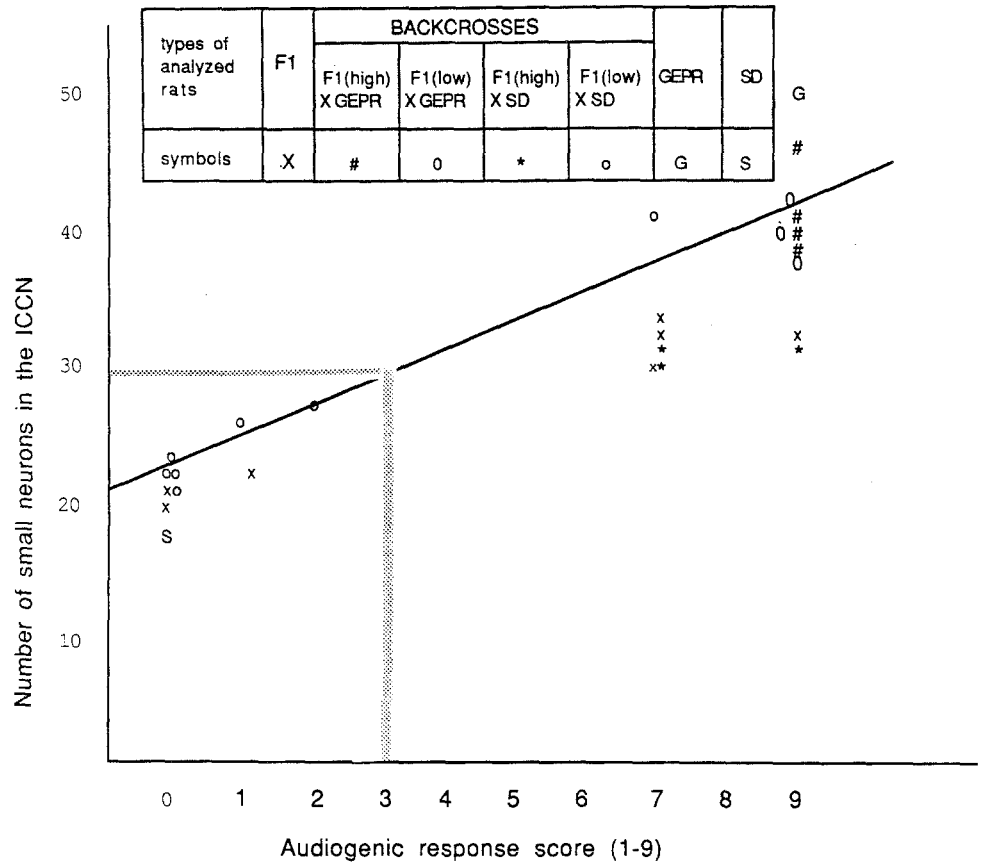

Fig. 11 A graph that shows the relationship between the number of small neurons in the ICCN and the audiogenic response scores of 28 rats. The coefficient of linear correlation was calculated to be 0.91, thus indicating that a significant correlation exists between audiogenic response score and small neuronal number in the ICCN. Note that the mean number of small cells in the ICCN obtained from three GEPR-3s *(shaded bars)* is located at a point on this correlation line that was predicted from the back-cross data. Published with permission from Ribak et al. (1988b)

and it may play a role in the generation of increased numbers of GABAergic neurons in the IC.

GEPRs display an abnormality in norepinephrine uptake. Since norepinephrine is present in lower levels in some brain regions in GEPRs than in SD rats, our laboratory, using immunocytochemistry, localized dopamine β-hydroxylase, the synthesizing enzyme for norepinephrine (Lauterborn and Ribak 1989). No difference in immunoreactive neurons or in fiber distribution was found in the cerebellum and locus coeruleus. Differences were found in the distribution of immunolabeled fibers for dopamine β-hydroxylase in the ICCN, thalamus, piriform, orbital and somatosensory cortices, and hippocampus in GEPR-9s. This study provided specific localization of deficiencies in the noradrenergic fiber plexus. Similarly, when the turnover rate of norepinephrine was examined in the thalamus, midbrain, pons-medulla and telencephalon, a decrease in norepinephrine was found in each of these areas (Jobe et al. 1984). Browning et al. (1989b) found a decrease in norepinephrine uptake in the cortex, hippocampus, amygdala, hypothalamus and IC of GEPR-9s. A reduction in the activity of dopamine β-hydroxylase was seen which correlated with the uptake of norepinephrine in the regions studied, suggesting a decrease in noradrenergic capability. When the concentration of serotonin was examined by Dailey et al. (1992) in 14 brain regions, including the IC, amygdala, hippocampus, frontal cortex, pons-medulla and thalamus, serotonin levels were found to be uniformly lower in GEPR-9s and also in GEPR-3s than in normal rats. This abnormality in the levels of serotonin in many brain regions may reflect a compromised serotoninergic capability in the brains of GEPRs.

Effects of knife cuts of the inferior colliculus

An analysis of the afferent and efferent pathways of the ICCN can provide further insight into the mechanisms for the propagation of seizure activity. A landmark study by Wada et al. (1970) showed that convulsants such as thiosemicarbazide, methionine sulfoximine, or metrazol did not cause seizure activity in animals whose IC had been bilaterally ablated, demonstrating the importance of the IC in AGS activity. Browning et al. (1985) found that lesions in the midbrain and pontine tegmentum ablated the tonic parts of the AGS in GEPR-9s. Similarly, lesions in the nucleus reticularis pontis oralis and pontine reticular formation attenuated seizure activity. Bilateral lesioning of the nucleus reticularis pontis oralis only abolished the clonic phase of the seizure in GEPRs exhibiting only the running seizure behavior (GEPR-3s). Browning (1986) later suggested that two distinct systems may be involved in AGS. One, the forebrain system, involves face and forelimb clonus, and the other, the brainstem system, is responsible for the running, bouncing, clonic and tonic parts of the seizure. Lesions in the dorsal hippocampus, caudate and intralaminar thalamic nuclei enhanced seizure severity.

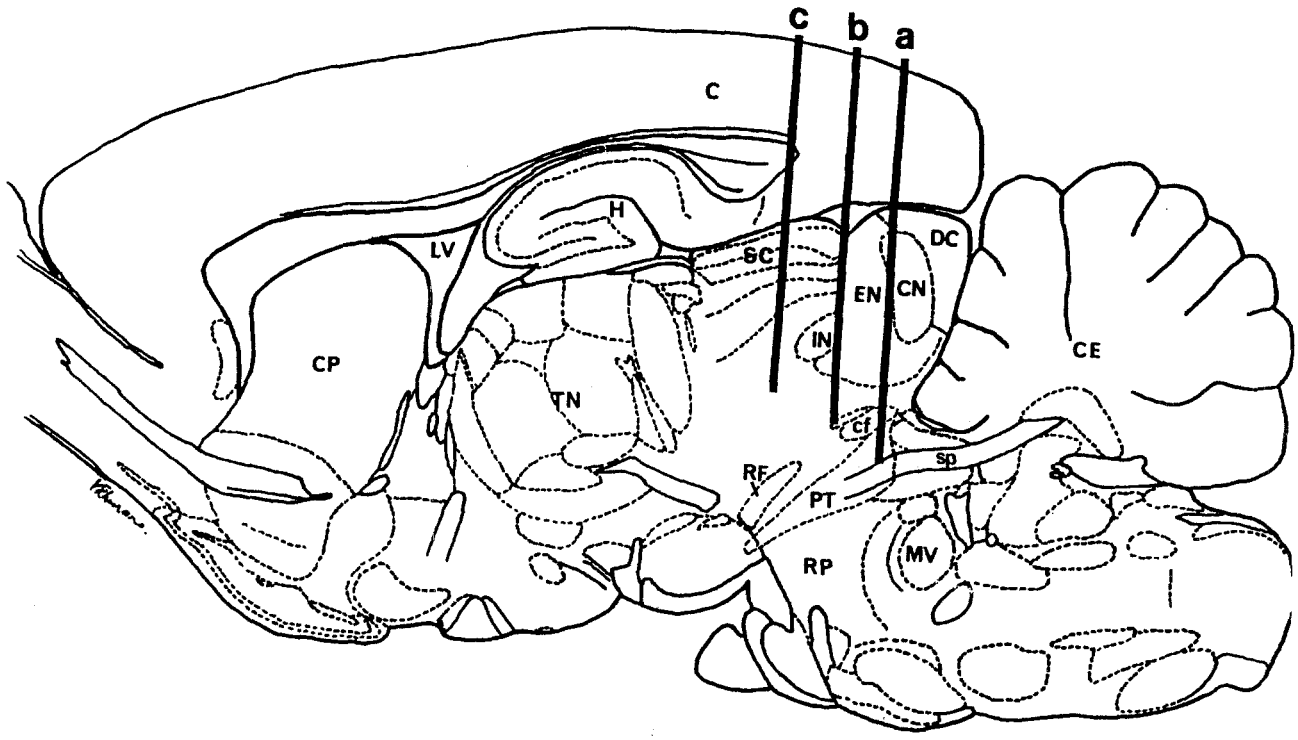

Fig. 12 Drawing of a parasagittal section to show the general locations of the lesions made in the coronal plane in the Ribak et al. study (1994). *Line a* indicates the location of lesions between the ICCN and the EN. *Line b* shows the site of intercollicular lesions. *Line c* indicates the site of lesions in the superior colliculus (*SC*). (*C* Cerebral cortex, *CE* cerebellum, *cf* cuneiform nucleus, *CN* central nucleus of IC, *CP* caudate-putamen, *DC* dorsal cortex of IC, *EN* external nucleus of IC, *H* hippocampus, *IN* intercollicular nucleus, *LV* lateral ventricle, *MV* motor trigeminal nucleus, *PT* pedunculopontine tegmental nucleus, *RF* retrorubral fields, *RP* reticular pontine oralis nucleus, *sp* superior cerebellar peduncle, *TN* thalamic nuclei)

A study was recently conducted in our laboratory to examine the effect of midbrain collicular knife cuts on AGS severity in the GEPR-9 (Ribak et al. 1994). We found that not only are seizures blocked by ICCN or lateral lemniscus lesions, but lesions between the external and central nuclei of the IC also blocked seizures (Fig. 12). Lesions between the IC and SC and lesions within the SC attenuated AGS activity (Fig. 12). These findings, along with the data obtained from horseradish peroxidase labeling after injection into the lesion site, indicated that projections from the central nucleus to the external nucleus of the IC and projections from the IC to the SC, both play a role in seizure propagation.

Functional significance

Seizure initiation

Data from several studies indicate that the ICCN is the site of initiation of seizure activity (Millan et al. 1986, 1988; Faingold et al. 1988; Ludvig and Moshé 1989). The increased numbers of GABAergic neurons and the observation that GABA acts as an inhibitory neurotransmitter in this structure appear to be inconsistent with the general view that decreased inhibition occurs at epileptic foci (see review by Ribak 1991). In another genetic model of epilepsy, increased numbers of GABAergic neurons were reported (Peterson et al. 1985). However, anatomical and physiological evidence has shown increased disinhibition of granule cells in the hippocampal dentate gyrus (Farias et al. 1992; Buckmaster and Schwartzkroin 1994). This hypothesis was tested with an electron microscopic analysis in GEPR-9s, but the data were not consistent with it, because the number of axosomatic synapses per soma in the ICCN of GEPR-9s was not different from that of SD rats (Roberts and Ribak 1988). Therefore, a different mechanism appears to be responsible for the initiation of seizure activity in the ICCN of GEPR-9s.

Evidence is accumulating for the hypothesis that the uptake of GABA is more efficient in the ICCN of GEPR-9s, and thus less GABA is available to interact with postsynaptic GABA receptors. The observations that the GABA transporter, GAT-1, is localized to GABA neurons in several brain regions (Brecha and Weigman 1994) and that increased numbers of GABA neurons exist in the ICCN of GEPR-9s are consistent with this hypothesis, originally proposed by Faingold et al. (1986a). Pharmacological evidence from studies using the GABA-uptake inhibitor tiagabine that was injected into the ICCN of GEPR-9s and blocked audiogenic seizures provides further support for this hypothesis (Faingold et al. 1994b). This hypothesis could also explain the fact that GABA applied to neurons in the ICCN was less effective in causing inhibition (Faingold et al. 1986a, b). Currently, anatomical studies to localize GABA trans-

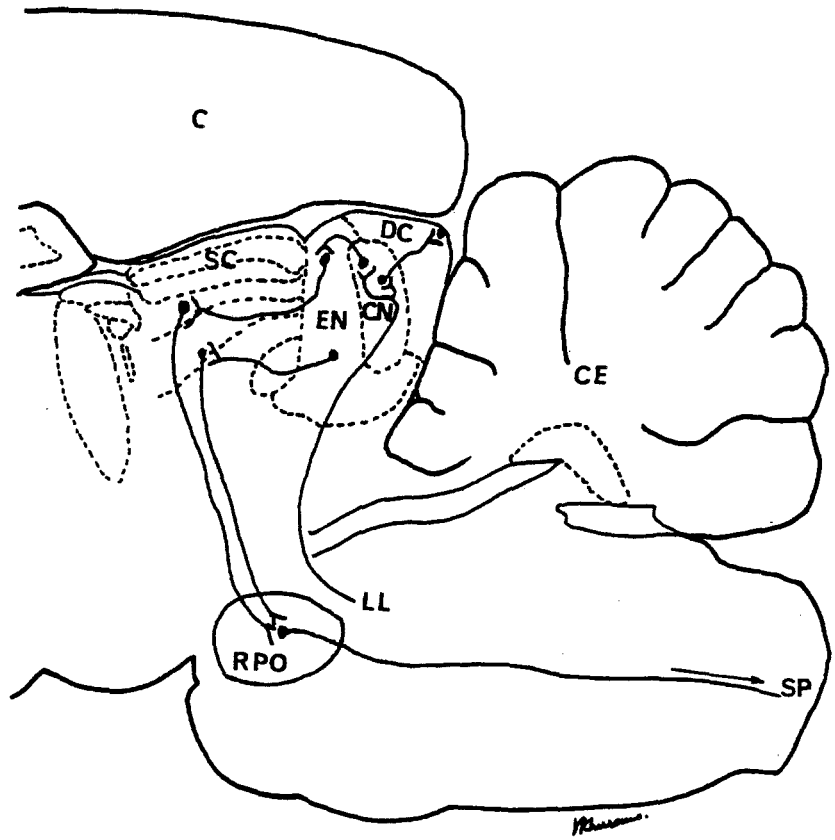

Fig. 13 Diagram of the proposed pathway for seizure propagation in GEPR-9s. Auditory stimulation increases the activity of fibers in the lateral lemniscus (*LL*) that terminate in the central nucleus (*CN*) of the IC. Initiation of seizure activity occurs in the CN, and the seizures propagate via projections to the EN and DC of the IC. Projections from these two regions terminate in the deep layers of the superior colliculus (*SC*) that have projections to the reticularis pontis oralis nucleus (*RPO*). This part of the reticular formation may activate motoneurons in the spinal cord (*SP*) for the final common pathway of seizure expression. Published with permission from Ribak et al. (1994)

porters in the ICCN are planned to determine whether the immunolabeling is greater in the GEPR-9s. The presence of more GABA transporter in GEPR-9s would suggest a faster rate of GABA uptake, and thus, less GABA would be present in the synapse after release from presynaptic axon terminals.

There is also the possibility of GABA receptor desensitization (see Faingold et al. 1994a, b). In this situation, GABA may interact with its receptor, but as a result of these abnormal long-term interactions, a down-regulation of the receptor may occur. This could lead to the same result, i.e., that GABA is less effective in producing inhibition in the ICCN. It is likely that phosphorylation of the GABA receptor may mediate this effect.

Another hypothesis to explain the initiation of seizure activity from the ICCN is that excitation is enhanced in the ICCN of GEPR-9s. An overexpression of glutamate receptors could provide the basis for this phenomenon (Seeburg 1993). This possibility is of particular interest because the ICCN of GEPR-9s shows increased levels of glutamate and aspartate (Chapman et al. 1986; Ribak et al. 1988a). Also, pharmacological data indicate that bilateral injections of glutamate agonists into the ICCN cause audiogenic seizure susceptibility in normal rats (Millan et al. 1986). If a glutamate receptor defect occurred in GEPR-9s, it would probably be genetically determined. The use of GEPR-3s would be important for this analysis in order to determine whether a similar, but lesser, defect in this receptor was present in this strain. Certainly, the use of GEPR-3s in the analysis of small cell numbers was helpful, because it showed data that were consistent with the correlation of small cells in the ICCN and audiogenic seizure severity (Ribak et al. 1988). A better understanding of the localization of glutamate receptor subunits in the ICCN to specific cell types will aid the testing of this hypothesis for a mechanism of seizure initiation in GEPRs.

Seizure propagation

The projection of the ICCN to the EN is an important part of the circuitry for seizure propagation in GEPR-9s. Both results from our study of lesions in the coronal plane (Ribak et al. 1994) and anatomical studies that show the ICCN projects bilaterally to the EN (Coleman and Clerici 1987; Saldaña and Merchán 1992) support the hypothesis that this pathway conveys seizure activity. Subsequently, seizure propagation passes along the output of the EN to the SC (Fig. 13). The deep layers of the SC receive this projection from EN, and it is these layers that have projections to the reticular pontine oralis nucleus that Browning (1986) has indicated plays a role in the tonic component of the seizures in GEPR-9s. Pertinent to this observation is the finding that bilateral injections of glutamate-blocking drugs into the pontine reticular formation significantly reduce AGS (Millan et al. 1988; Faingold et al. 1992). Severing of the connection between the EN and SC has been shown to decrease substantially audiogenic-like seizures in both GEPR-9s and

rats injected with bicuculline into the IC (Tsutsui et al. 1992; Ribak et al. 1994). These data show the importance of the connection between the IC and SC for the propagation of seizure activity in audiogenic seizures. The analysis of other brainstem structures in audiogenic seizures is required because recent data indicate that increased levels of fos immunoreactivity are found in the periaqueductal gray after audiogenic seizures in GEPR-9s (Chakravarty et al. 1993). The use of other anatomical methods may demonstrate the involvement of this structure as well as several others. Further studies are required to determine the relationship of these other structures to the propagation of seizure activity in the brain of GEPRs.

Conclusions

This review provides a summary of the data that show a role for the IC in audiogenic seizures. The detailed anatomical analyses of cell types and connections of the ICCN are extremely important for our understanding of the basic mechanism of initiation of seizure activity in this genetic model. Two hypotheses will be tested in future studies: (1) increased GABA uptake, and (2) increased glutamate receptor expression. A better knowledge of the cell types and their local circuitry and interactions through combined intracellular electrophysiology and labeling will aid in this analysis. The studies of seizure propagation will rely on functional mapping studies that will show the brain regions that are excited following the initiation of seizures in the ICCN. Together, these future studies will provide important new data about the structural and functional role of the IC in epilepsy.

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