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Authors
Peterson, GM
Ribak, CE

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Chapter 24

Evidence for supernumerary GABAergic neurons and disinhibition in the hippocampus of seizure-sensitive gerbils

Gary M. Peterson[1] and Charles E. Ribak[2]

[1]*Department of Anatomy & Cell Biology, East Carolina University School of Medicine, Greenville, North Carolina 27858, USA; and* [2]*Department of Anatomy & Neurobiology, University of California, Irvine, Irvine, California 92717, USA*

Mongolian gerbils (*Meriones unguiculatus*) provide a useful animal model for the study of epilepsy because they exhibit clonic-tonic seizures which resemble human secondarily generalized seizures (Thiessen *et al.*, 1968; Loskota *et al.*, 1974) with a focal onset. Seizures are induced by a number of sensory stimuli but exposure to a novel environment seems to be the best inducer (Loskota *et al.*, 1974; Ludvig *et al.*, 1991). The intensity of seizure varies within the gerbil population but is relatively constant for individual animals so that it is therefore possible to correlate a known history of seizure intensity with morphological observations. A typically intense seizure lasts several minutes and begins with whisker twitching, eye blinking, and flattening of the pinnae. This rapidly evolves into lordosis, followed by wild jumping and running and then by loss of righting, whole body tonus, and clonic movements of the forelimbs. After 1–2 min, the animal rights itself but maintains a frozen posture while exhibiting facial movements. This postictal phase lasts for at least another 2 min. Within the wild-type population seizures occur in about 50 per cent of gerbils, but the frequency can be increased by selective breeding. The animals used in our studies had been bred phenotypically to produce two strains, one which is seizure-sensitive and one which is seizure-resistant. Since the onset of seizure activity does not begin until about 50 days of age (Loskota *et al.*, 1974), it is possible to examine the brains of young 'seizure-predisposed' progeny of seizure-sensitive animals prior to the occurrence of seizure activity to determine if the differences between seizure-sensitive and seizure-resistant brains occur prior to seizure onset or are the result of seizure activity.

Abnormalities within the GABAergic system have been implicated in the seizure sensitivity of gerbils. For example, when GABA levels are increased in seizure-sensitive gerbils by the administration of GABA agonist drugs, seizure susceptibility is reduced and the dose required for this effect is significantly smaller than that required for other genetically predisposed animals or animals with chemically- or electrically-induced seizures (Löscher, 1984; Löscher *et al.*, 1983). Furthermore, all three categories of GABA mimetic drugs (GABA agonists, GABA-T inhibitors, and inhibitors of

GABA uptake) are highly effective in suppressing seizures in gerbils. This efficacy suggests that the seizure susceptibility results, at least in part, from impairment of GABA-mediated neurotransmission.

Several lines of evidence indicate that the hippocampus is involved in seizure activity. These include electroencephalographic recording, alterations in seizure following lesions to hippocampal pathways, and morphological changes within the hippocampus after seizure activity. Majkowski & Donadio (1984) showed hippocampal electrographic activity during the clonic–tonic phase of the seizure, but concluded that the seizure began in the frontal cortex. The role of the hippocampal formation in seizure activity was also examined following lesions of its input and output. Bilateral transection of the perforant path, which provides the hippocampal formation with its primary excitatory input, results in the abolition of the behavioural expression of seizure activity whereas unilateral transection of the perforant path or bilateral transection of the fornix resulted in no change or an increase in seizure intensity (Table 1; Ribak & Khan, 1987). A reduction in the number of pyramidal cells (Mouritzen Dam *et al.*, 1981) and diminished density of spines on the proximal portion of their apical dendrites (Paul *et al.*, 1981) was shown. In the latter study, the examined dendritic region is known to be contacted by mossy fibre terminals arising from the dentate granule cells. We (Peterson *et al.*, 1985) subsequently showed that the terminals of these mossy fibres (mossy tufts) were dramatically depleted of synaptic vesicles, had increased numbers of cisternae of agranular reticulum, and had numerous mitochondria in close proximity to the synaptic zone immediately after seizure (Fig. 1). Because these features are indicative of a high rate of synaptic activity (Nitsch & Rinne, 1981) we suggested that the granule cells in seizure-sensitive gerbils are more active, perhaps due to disinhibition. Our light and electron microscopic examination of GABAergic neurons and their terminals in the dentate gyrus and Ammon's horn was designed to test this hypothesis.

Table 1. Effects of transection of the major input and output pathways of the hippocampal formation on seizure expression. Note that bilateral transection of the perforant path, the major input pathway, completely abolished behavioural evidence of seizure (data from Ribak & Khan, 1987).

Lesion	Mean seizure score	
	Before	After
Bilateral fornix + perforant path	3.2	0
Bilateral perforant path	2.5	0
Bilateral fornix	1.7	2.6
Unilateral perforant path	2.7	3.3
Sham	3.1	3.3

Methods

Animals

The adult gerbils used in our studies were provided by Scheibel & Paul and originated from the colony of Lomax & Loskota (see Loskota *et al.*, 1974). The seizure-sensitive animals had been selectively bred for seizure sensitivity for over 15 generations and the seizure-resistant gerbils had been selectively bred for seizure resistance for at least 10 generations. Adult animals of both sexes and strains were tested once a week for seizure sensitivity and intensity of seizure. The testing procedure involved placing the animals, one at a time, into an empty stainless steel box for 5 min or until they had a seizure. Seizure intensity was rated on a five point scale from 0 to 4 that was modified from

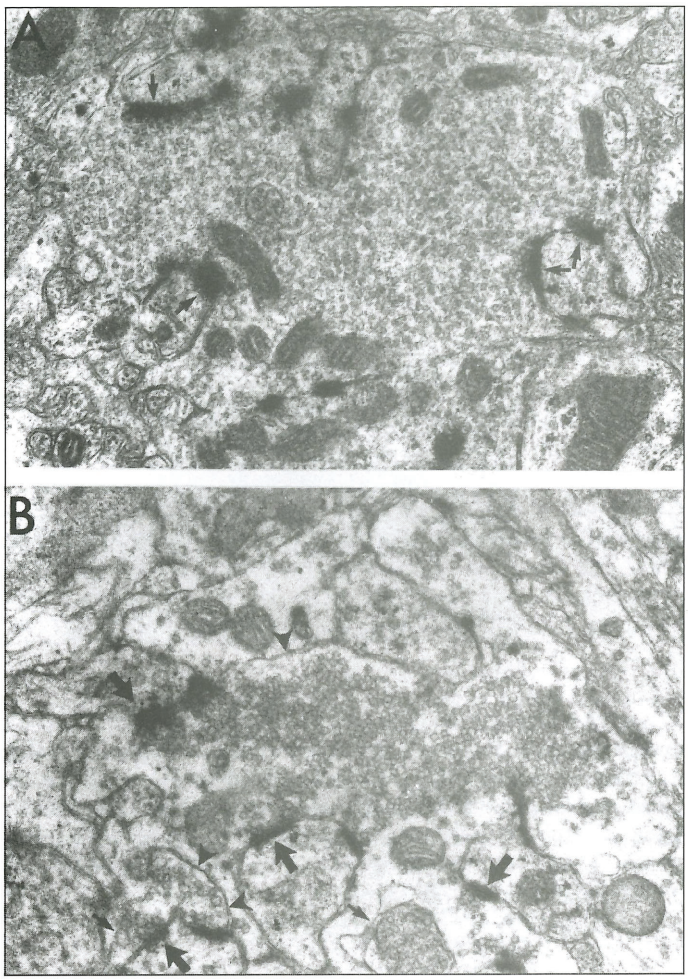

Fig. 1. A: Electron micrograph of a mossy tuft from a seizure-resistant brain. Round synaptic vesicles fill most of this terminal that forms typical asymmetric axospinous synapses (arrows). 21,000X. B: A mossy tuft from a seizure-sensitive brain. This terminal displays a depletion of synaptic vesicles, membrane infoldings derived from active sites (arrowheads) and cisternae of agranular reticulum (arrows). These features are typical for 'active' terminals. Asymmetric axospinous synapses (large arrows) are also formed by seizure-sensitive mossy tufts. 24,000X. (Reproduced from Peterson et al., 1985, with permission of the publisher.)

Loskota *et al.* (1974). A zero score was given when no seizure was observed. A score of one indicated a mild seizure in which vibrissae twitching and some flattening and flicking of the pinna were observed. A score of 2 was given if the twitching of vibrissae and pinnae occurred with motor arrest. A 3 indicated a gerbil with the same features as in 2 but with myoclonic jerks. Lastly, a 4 indicated a severe seizure in which the animal manifested clonic–tonic forepaw movements (forelimb jerking, followed by tonic extension), head bobbing, extreme lordosis and falling, followed by righting, wild running and jumping. None of the gerbils died following a seizure. After a seizure, the gerbils would often enter a post-ictal state for 2 min or more during which they exhibited behaviour characteristic of limbic seizures. The progeny of seizure-sensitive gerbils, the 'seizure-prone' gerbils, were not subjected to this testing because they were analysed with histological methods at 25 to 30 days of age, an age prior to the onset of seizure activity.

Histology

Animals were deeply anesthetized with pentobarbital and transcardially perfused for fixation of brain tissue. For light microscopic examination, fixation was by buffered 4 per cent paraformaldehyde. After cryoprotection in buffered 25 per cent sucrose, brains were cut in the coronal plane at a thickness of 40 µm and collected into five sets of a one-in-five series. One set of sections was stained with cresyl violet to provide Nissl staining and an adjacent set was stained immunocytochemically for glutamic acid decarboxylase (GAD; Oertel *et al.*, 1981a, b) as a marker for GABAergic neurons. Details of the staining procedures have been described previously (Peterson & Ribak, 1987). When possible, seizure-sensitive, seizure-resistant and seizure-prone brain sections were processed simultaneously. For electron microscopic examination, fixation was according to the method of Friedrich & Mugnaini (1981) as described by Farias *et al.* (1992).

Cell counting

The number of GAD-immunoreactive neurons in various regions was determined within individual sections. GAD-immunoreactive somata were counted in six seizure-sensitive, four seizure-resistant and three seizure-prone brains in the hippocampus, dentate gyrus, motor cortex, substantia nigra and nucleus reticularis thalami. Within the hippocampus, counts were made in six subdivisions: three in regio superior (CA1; strata oriens, pyramidale and radiatum-lacunosum-moleculare) and three in regio inferior (CA2,3; strata oriens, pyramidale and lucidum-radiatum-lacunosum-moleculare). The dentate gyrus was subdivided into five parts: the hilar region and the supra- and infrapyramidal blades of strata granulosum and moleculare, respectively. In the hippocampus and dentate gyrus every fifth section along the entire septotemporal axis was analysed. To standardize the data for variations in the sizes of strata granulosum and moleculare of the dentate gyrus, area measurements were made by tracing each of the lamina onto the digitizing tablet of a Bioquant Image Analysis System (R & M Biometrics) and relative cell counts were converted to cell densities. Since these data were not used to estimate the total number of neurons in any of the brain regions studied but rather the relative number per section, it was not necessary to use a split-cell correction factor. The size of GAD-immunoreactive somata within the dentate gyrus and hippocampus was calculated by computer-assisted image analysis (Bioquant, R & M Biometrics). Counts of GAD-immunoreactive neurons were also made in the motor cortex throughout all cortical layers from several traverses between the pial surface and the white matter. In addition, cell counts were made throughout the rostral 1000 μm of the substantia nigra, and cell density measurements for the reticular nucleus of the thalamus were made from equivalent regions of known area.

Synaptic interactions

In addition to the counts of GAD-immunoreactive neuronal somata, GAD-immunoreactive puncta (the presumed light microscopic analog of synaptic terminals (Ribak *et al.*, 1981; Oertel *et al.*, 1981b)) were counted in thick and semi-thin sections of the dentate gyrus stratum granulosum using a 100x oil immersion objective and an eye-piece grid reticule. A region approximately 100 μm lateral to the crest of stratum granulosum was sampled in both the supra- and infrapyramidal blades approximately 1200 μm caudal to the septal pole of the dentate gyrus which was within the septal third of its long axis. Similar regions were sampled for electron microscopic examination and counts were made of asymmetric and symmetric synapses on somata of GAD-immunoreactive basket cells and non-immunoreactive granule cells.

Statistics

To determine whether significant differences existed between the data groups obtained from seizure-sensitive, seizure-resistant and seizure-prone gerbils, a one way analysis of variance for these groups was initially used. When the sample populations were small, a non-parametric test, the Kruskal-Wallis method, was employed. If significant differences were found between the groups, then an unpaired t-test or a Mann-Whitney U-test was used to determine which groups were responsible for the differences. Differences were expressed relative to the seizure-resistant gerbils which are generally considered a control group.

Results

Analysis of GABAergic neurons

Dentate gyrus

The size and distribution of GAD-immunoreactive somata in the seizure-resistant dentate gyrus was similar to that in the rat; the spacing between adjacent cells was usually 80–140 μm and they were only rarely found in close proximity to one another. In contrast, GAD-immunoreactive somata in the

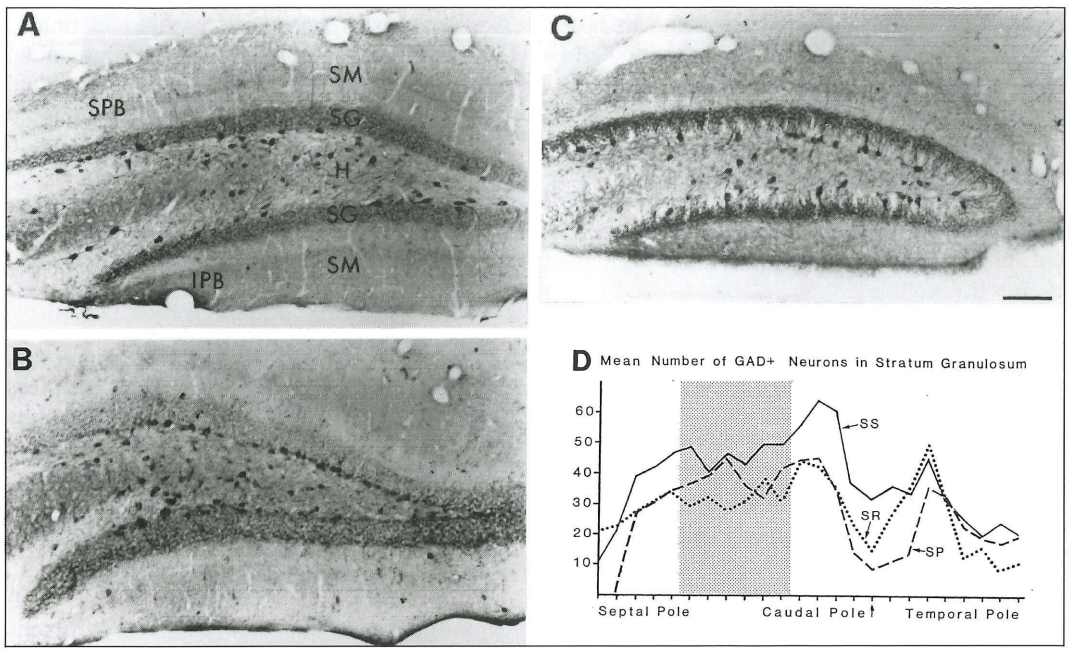

Fig. 2. Coronal sections which were incubated in antiserum to GAD to show the somal distribution of GABAergic neurons in the gerbil dentate gyrus. GABAergic pyramidal basket cells in the seizure-resistant dentate gyrus (A) are found at the border between the stratum granulosum (SG) and the hilus (H) in both the suprapyramidal (SPB) and infrapyramidal (IPB) blades. SM = stratum moleculare. Both seizure-sensitive (B) and seizure-prone (C) dentate gyri display more GABAergic neurons at this location than those from seizure-resistant brains. Counts from the hilus and stratum moleculare also showed increases in the seizure-sensitive brains (see text). Scale bar = 100 μm. D. Graphic representation of the mean number of GAD-immunoreactive neurons in the dentate gyrus of seizure-sensitive, seizure-resistant and seizure-prone gerbils. The septotemporal axis has been displayed in a linear fashion so that variations in cell number along this axis can be identified. The position of the septal, caudal and temporal poles of the dentate gyrus are indicated. Only the data for the suprapyramidal blade are shown. The shading indicates the septal region where the differences between seizure-sensitive and seizure-resistant gerbils were most substantial. (A, B, and C are reproduced from Peterson et al., 1985, with permission of the publisher. D is reproduced from Peterson & Ribak, 1987, with permission of the publisher.)

seizure-sensitive dentate gyrus often formed groups of three or four where some appeared to contact each other. In addition, the average size of the GAD-immunoreactive somata in the seizure-sensitive dentate gyrus was 30 per cent smaller than in the seizure-resistant dentate gyrus ($\bar{x}_{\text{seizure-sensitive}} = 112.6$ μm^2, $\bar{x}_{\text{seizure-resistant}} = 144.1$ μm^2, $P < 0.01$, Student's *t*-test). The most striking difference between the seizure-resistant and seizure-sensitive dentate gyri was the number of GAD-immunoreactive somata, especially those contained within or having processes passing through the stratum granulosum (Fig. 2). In some cases there were nearly twice as many cells in the suprapyramidal blade of the seizure-sensitive brains as compared to the corresponding region of seizure-resistant brains. Across all animals there was a statistically significant 35 per cent increase in the total number of GAD-immunoreactive neurons in the suprapyramidal blade of seizure-sensitive brains as compared to seizure-resistant brains ($P < 0.05$, Mann-Whitney U-Test). The difference was most substantial and consistent in the septal half of the dentate gyrus (Fig. 2D) in which significant differences were also observed (unpaired t-test, seizure-sensitive vs. seizure-resistant, $P < 0.05$ and seizure-sensitive vs. seizure-prone, $P < 0.05$). Within the infrapyramidal blade the number of GAD-immunoreactive

neurons was approximately the same in both the seizure-sensitive and seizure-resistant brains. Regression analysis showed that the number of GAD-immunoreactive neurons in the suprapyramidal blade of the stratum granulosum was positively correlated with the intensity score of the individual animal's seizure record (r = 0.725). As in stratum granulosum, stratum moleculare had more GAD-immunoreactive neurons in seizure-sensitive brains than in seizure-resistant brains and again the difference was most pronounced in the suprapyramidal blade. Even the number of GAD-immunoreactive cells in the seizure-sensitive hilus was approximately 20 per cent greater than in the seizure-resistant. Thus, seizure-sensitive brains displayed more GAD-immunoreactive somata than did seizure-resistant brains in all three regions of the dentate gyrus. This difference was maintained even when cell counts were standardized by converting counts to cell density (number of GAD-immunoreactive somata/mm^2).

In general, the brains of the young offspring of seizure-sensitive gerbils, the seizure-prone group, displayed more GAD-immunoreactive neurons than the seizure-resistant brains but somewhat less than the seizure-sensitive brains. After correcting for differences in size by converting raw cell counts to cell densities some of the seizure-prone brains were found to have similar GABAergic neuronal densities to the seizure-sensitive brains. Furthermore, with this calculation, all seizure-prone brains had densities greater than the seizure-resistant brains. The variation in seizure-prone data may reflect the variation that is known to occur in the seizure records of the offspring of seizure-sensitive gerbils.

Ammon's horn

GAD-immunoreactive neurons were found in all subregions within the hippocampus except the alveus and they varied in size, ranging from 13 to 20 μm in diameter. Those cells that showed staining of the proximal dendrites could be characterized as either multipolar or fusiform. The major difference in the number of GAD-immunoreactive somata in the hippocampus occurred in the CA2,3 region where an overall increase of 42 per cent was observed in seizure-sensitive gerbils as compared to seizure-resistant gerbils. The most pronounced difference and the only one that was statistically significant between groups ($P < 0.05$, Kruskal-Wallis method) occurred between seizure-sensitive and seizure-resistant gerbils (65 per cent, $P < 0.05$, unpaired t-test) and was observed in the CA2,3 apical dendritic field which consisted of the strata lucidum, radiatum and lacunosum-moleculare. The CA1 region of seizure-sensitive brains showed a small (10–15 per cent) increase in the number of GAD-immunoreactive cells, but it was not statistically significant. In seizure-prone gerbil brains an overall increase of 10 per cent was observed in the number of GAD-immunoreactive neurons in all regions of the hippocampus when compared with seizure-resistant brains. This difference was not statistically significant. Again, the greatest difference (23 per cent) was noted in the apical dendritic field of the CA2,3 pyramidal cells. In general, the numbers for seizure-prone gerbils were intermediate between the counts for seizure-sensitive and seizure-resistant gerbils.

Other brain regions

GAD-immunoreactive neurons were examined in the substantia nigra, reticular nucleus of the thalamus, and motor cortex from seizure-sensitive and seizure-resistant gerbils. These regions represent areas which are either rich in GABAergic neurons or have been implicated in seizure activity or both. No differences in terminal or somal staining were noted between seizure-sensitive and seizure-resistant gerbils, nor did the number or size of GAD-immunoreactive neurons differ between the two strains in any of these regions.

Analysis of synaptic contacts between GABAergic cells in the dentate gyrus

The distribution of GAD-immunoreactive puncta (previously shown to correspond to axon terminals) within the seizure-resistant dentate gyrus was similar to that reported in the rat (Barber & Saito, 1976; Ribak *et al.*, 1981; Goldowitz *et al.*, 1982; Seress & Ribak, 1983). Thus, the outer third of stratum moleculare was moderately dense and the density of puncta in stratum granulosum was uniform

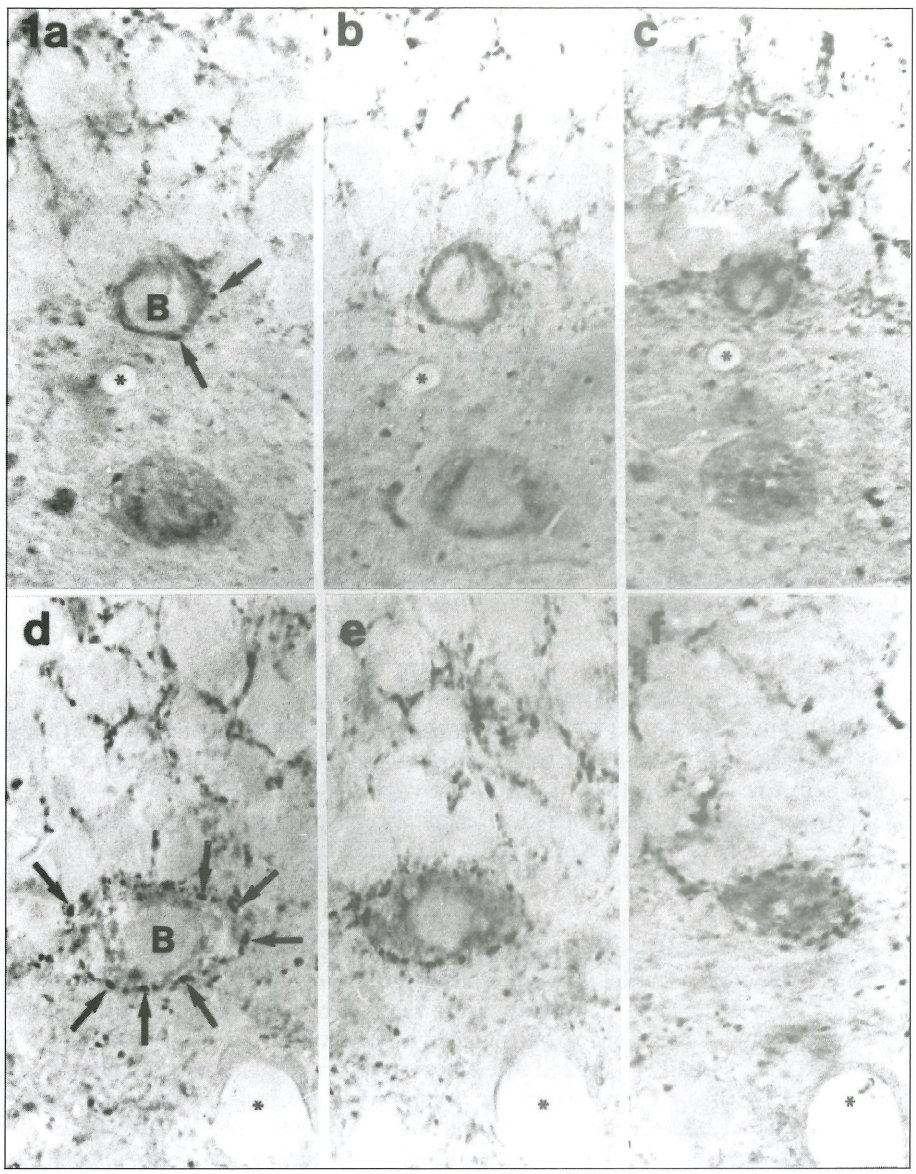

Fig. 3. Photomicrographs of serial semithin sections (1 μm thick) that show GAD-immunoreactive basket cells (B) in the dentate gyrus of seizure-resistant (a–c) and seizure-sensitive (d–f) gerbils. The somata of these GABAergic basket cells are found on the hilar border with the granule cell layer. The number of GAD-immunoreactive puncta (arrows) adjacent to the seizure-resistant basket cell body (a) is less than that for the seizure-sensitive gerbil basket cell (d). Note that few, if any, GAD-immunoreactive puncta are found on the basal surface of seizure-resistant basket cell somata (a–c). In contrast, the seizure-sensitive gerbil basket cell (d–f) displays many GAD-immunoreactive puncta apposed to its basal surface. The number of GAD-immunoreactive puncta around the somata of granule cells located above the basket cells (B) appears to be similar for both types of gerbil. A capillary (*) is indicated for orientation in each set of three panels. Scale bar = 10 μm. (Reproduced from Farias et al., 1992, with permission of the publisher.)

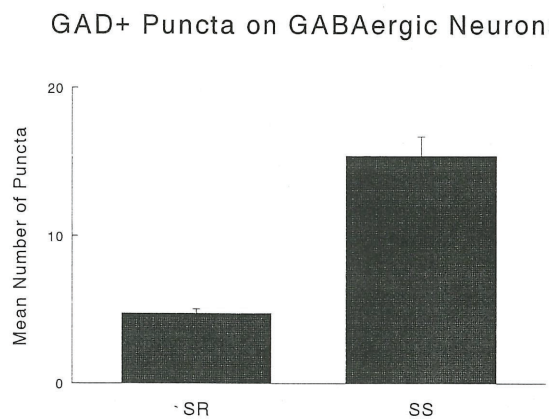

Fig. 4. Histogram showing the mean number of GAD-immunoreactive puncta around GAD-immunoreactive basket cells in the dentate gyrus of seizure-resistant and seizure-sensitive gerbils. In seizure-resistant brains 460 GAD-immunoreactive puncta were found around 97 GAD-immunoreactive basket cells. In seizure-sensitive brains 618 GAD-immunoreactive puncta were found around 39 GAD-immunoreactive basket cells. The difference is significant at $P < 0.0005$ (unpaired t-test with 135 df).
Data are from Farias et al. (1992).

between the infra- and suprapyramidal blades. In contrast, the density of GAD-immunoreactive puncta in the seizure-sensitive dentate gyrus was approximately three times greater in the infrapyramidal blade of stratum granulosum than in the suprapyramidal blade. The density of puncta in both blades of the seizure-sensitive dentate gyrus was significantly greater than in the seizure-resistant ($P < 0.01$; Student's t-test), and the GAD-immunoreactive terminals appeared to be both larger and more densely stained in the seizure-sensitive brains, especially in the infrapyramidal blade. No differences were observed in the density of GAD-immunoreactive puncta within stratum moleculare either between blades or between strains.

Light microscopic analysis of semi-thin sections showed that GAD-immunoreactive cells in the suprapyramidal blade from seizure-resistant gerbils had relatively few GAD-immunoreactive puncta adjacent to their somata (Figs. 3a–c, 4). In contrast, sections from seizure-sensitive gerbils showed numerous GAD-immunoreactive puncta surrounding GAD-immunoreactive somata (Figs. 3d–e, 4). These differences were partially confirmed by electron microscopic analysis of numbers of asymmetric (excitatory, non-GABAergic) and symmetric (inhibitory, GABAergic) synapses on to the somata of GAD-immunoreactive basket cells and non-immunoreactive granule cells. The basket cells ($n = 9$) from seizure-sensitive gerbils had more symmetric synapses per unit length of somal surface than those ($n = 4$) from seizure-resistant gerbils. In contrast, there were no differences in the numbers of asymmetric synapses between basket cells from seizure-sensitive and seizure-resistant gerbils. Granule cell somata from seizure-sensitive ($n = 42$) and seizure-resistant ($n = 26$) gerbils showed no differences in the number of either asymmetric or symmetric synapses.

Discussion

Taken together, our data suggest that the hippocampal formation of seizure-sensitive gerbils has an abnormal circuitry that is involved in the generation and/or propagation of epileptic activity. Not only is the number of GABAergic neurons increased, but the number of GABAergic synapses on to GABAergic somata is also increased in both seizure-sensitive and seizure-prone gerbils. Furthermore,

the increased numbers of GABAergic neurons have been observed only in the dentate gyrus and hippocampus, and these appear to be interconnected in an aberrant fashion.

The differences between the seizure-sensitive and seizure-resistant hippocampus do not appear to be the result of compensatory changes following seizure activity because the hippocampus of young seizure-sensitive progeny (seizure-prone) which had not had seizures also showed increased numbers of GABAergic cells. Thus, it would appear that the differences between the two strains is genetically related. Another important finding was the correlation between the number of GABAergic neurons in the dentate gyrus and the individual gerbil's seizure intensity. This correlation suggests that the severity of seizure activity is related to this abnormality.

Hippocampal disinhibition hypothesis

We have proposed an hypothesis of disinhibition which explains the apparent contradiction between the occurrence of seizure activity including vesicle depletion in mossy terminals and the increased numbers of inhibitory structures (GABAergic somata and terminals) in the hippocampal formation. GABAergic basket cells in the hippocampal formation receive collateral input from the excitatory granule and pyramidal cells (Frotscher, 1985; Ribak & Seress, 1983). The GABAergic cells in turn form pericellular basket plexuses around the granule cell somata and form axosomatic connections (Ribak & Seress, 1983; Seress & Ribak, 1985). Thus, the GABAergic cells provide feed-back inhibition to the granule cells of the dentate gyrus and pyramidal cells of the hippocampus (Andersen, 1975). In the non-epileptic hippocampal formation feed-back inhibition is responsible for controlling the output of the granule and pyramidal cells. Our morphological observations have shown that the number of GABAergic neurons and the number of inhibitory synaptic connections onto GABAergic somata are increased in the dentate gyrus of the seizure-sensitive gerbils. The normal feed-back circuit and our proposed abnormal circuitry is illustrated in Fig. 5. Activation of such a circuit by the collateral input from the excitatory cells would cause one of the inhibitory neurons to inhibit the other, thereby effectively blocking the feed-back inhibition or inducing *dis*inhibition.

The observation that increased GABA levels suppress seizures in epileptic gerbils (Löscher, 1984; Löscher *et al.*, 1983) would appear to be contradictory to our hypothesis of disinhibition within the

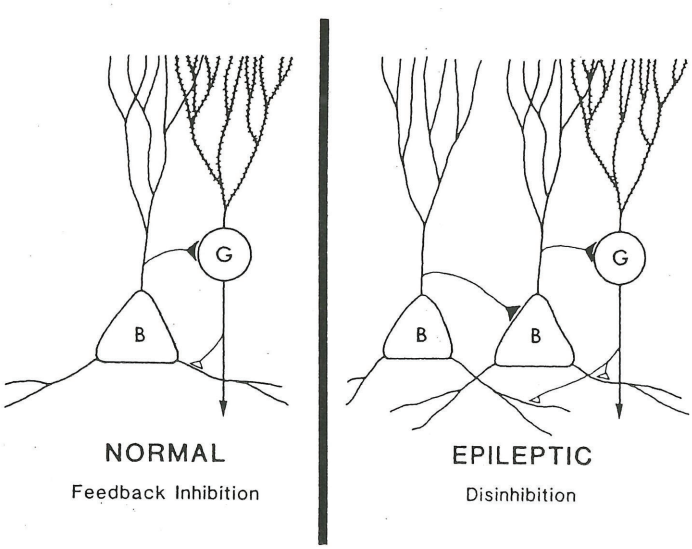

Fig. 5. Schematic diagram of the circuitry between granule and basket (GABAergic) cells in the dentate gyrus from seizure-resistant (left) and seizure-sensitive (right) gerbils. In seizure-resistant gerbils, axon collaterals of granule cells (G) form excitatory synapses with the basal dendrites of basket cells (B), which send inhibitory axons to the soma of the granule cell. This circuitry provides a normal feedback inhibition. In contrast, the seizure-sensitive gerbils have additional basket cells (B) that inhibit other basket cells that contact the granule cells (G), thereby resulting in disinhibition of the granule cells.

dentate gyrus. According to our hypothesis, increased GABA levels (at the synapses between GABAergic cells) would be predicted to increase disinhibition and thereby increase excitation (and presumably seizure activity). It is likely, however, that the systemic administration of GABA agonists and GABA mimetics used in the studies of Löscher and colleagues affects all regions of the brain and not just the contacts between GABAergic cells in the dentate gyrus. Thus, even though disinhibition might be increased within the dentate gyrus, the overall effect of these drugs on cortical and limbic brain structures would be increased inhibition resulting in reduced susceptibility to seizure.

Although GABA is usually associated with postsynaptic hyperpolarization and inhibition (Mody *et al.*, 1994), GABA has been shown to evoke excitatory responses in a subpopulation of neurons in the dentate hilus (Michelson & Wong, 1991, 1994). It is conceivable that the aberrant synaptic contacts that we have shown between GABAergic neurons in the dentate gyrus of the seizure-sensitive gerbil may be coupled by such excitatory synaptic contacts. However, the GABAergic cells which we have shown to be interconnected are within the granule cell layer whereas those studied by Michelson & Wong are in the hilus; furthermore, they studied guinea pig rather than gerbil. Finally, in their studies, they found that the net result of GABA-mediated excitation of hilar interneurons was synchronized and large amplitude inhibitory postsynaptic potentials in granule and pyramidal cells. Since electrophysiological data for GABAergic basket cells in gerbils are lacking, we assumed the traditional inhibitory effect in advancing our disinhibition hypothesis, i.e. the physiological effect of the supernumerary synapses with basket cells is to inhibit the basket cells and thus disinhibit granule cells. Consistent with this proposal is the finding by Farias *et al.* (1992) that removal of the entorhinal excitatory drive to this abnormal circuit in seizure-sensitive gerbils is associated with quiescent or normal looking mossy fibre terminals. In fact, electrophysiological data on the gerbil hippocampus (Buckmaster & Schwartzkroin, 1994) indicate that the dentate gyrus displays hyperexcitability. More detailed analyses are required to confirm the disinhibition hypothesis.

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