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A Possible Role for Beta-Adrenergic Receptors in the Expression of Audiogenic Seizures[1]

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LINTS, C. E. AND C. NYQUIST-BATTIE. *A possible role for beta-adrenergic receptors in the expression of audiogenic seizures.* PHARMACOL BIOCHEM BEHAV 22(5) 711–716, 1985.—DBA/2 mice are genetically prone to audiogenic seizures and, when compared with seizure resistant C57BL/6 mice, were found to have an increased density of β-adrenergic receptors in their midbrain at the age of peak seizure susceptibility. Propranolol, a β-receptor blocking agent, attenuated all stages of the seizure syndrome. However, a comparison of the effects of its d- and l-isomers suggested that propranolol's anticonvulsant activity was due to its local anesthetic-like action. Pindolol, a more potent beta blocker that is at least 100 times less potent than propranolol with respect to local anesthetic-like activity, produced anticonvulsant effects in approximately the same systemic dose range as propranolol. This indicates that pindolol's anticonvulsant activity could be due to beta blockade and, taken together, these data suggest that β-adrenergic receptors may play a role in the expression of audiogenic seizures in these animals.

Audiogenic seizures β-Adrenergic receptors Propranolol Pindolol Epilepsy

THE importance of genetic determinants as contributing factors in human epilepsy emphasizes the relevance of genetic models for studies of epileptogenic mechanisms [21]. Mice of the DBA/2 strain are genetically prone to audiogenic seizures (AGS) during an early stage of their development. When exposed to an intense sound they usually show the full AGS syndrome, which progresses from wild running attacks to clonic, and then tonic convulsions which frequently result in death due to anoxia [28,29]. Although some abnormality of brain noradrenergic transmission is thought to play a role in the expression of AGS in these animals, the evidence for the nature of this role is inconsistent and difficult to interpret. Most studies have either manipulated and/or measured endogenous brain levels of norepinephrine (NE), or measured the activity of enzymes regulating these levels, and related the results to differences in AGS susceptibility [12, 13, 16, 23, 24, 25]. Since very few reports have focused directly on noradrenergic receptor mechanisms, Experiment 1 of the present study was designed to measure β-adrenergic receptor densities and binding characteristics in the brains of DBA mice at their age of peak AGS susceptibility and compare them with those of like-aged seizure resistant C57BL/6 mice. The positive finding of an increased density of β-adrenergic receptors in the DBA midbrain let to Experiments 2, 3, and 4, that tested the anticonvulsant activity of the β-receptor blocking agents propranolol and pindolol in these animals. These experiments attempted to provide evidence for a relationship between β-adrenergic receptors and AGS susceptibility.

EXPERIMENT 1: BETA-NORADRENERGIC RECEPTOR DENSITIES AND AFFINITIES IN THE BRAINS OF AGS SUSCEPTIBLE AND NONSUSCEPTIBLE MICE

Using [3H]-dihydroalprenolol (DHA), β-adrenergic receptor densities and affinities were measured on membrane fractions obtained from three brain regions of the seizure susceptible DBA/2 mice at their age of peak AGS susceptibility, and from like-aged nonsusceptible C57BL/6 mice. No attempt was made to differentiate between β-1 and β-2 receptor subtypes [19] as the methods would have required large amounts of brain tissue.

METHOD

Subjects

The subjects were experimentally naive 19–23 day old DBA/2 and C57BL/6 mice of both sexes who were the offspring of stock obtained from the Jackson Laboratory, and were bred and reared in the Northern Illinois University Psychology Department mouse colony in controlled lighting (12 hr light/12 hr dark) and a moderate acoustic environment. The animals were weaned on the day of sacrifice.

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Biochemical Procedures

All animals were sacrificed by decapitation between 2–4 p.m. Their brains were quickly removed and the three regions used in the assays were dissected out under a magnifying lens. First the middle cerebellar peduncle was cut bilaterally at its junction with the cerebellum, and the cerebellum was removed from the brain stem. The lower brain stem was separated from the midbrain by a transverse section at the caudal border of the inferior colliculus and discarded. The midbrain was then removed by a transverse section at the rostral border of the superior colliculus. Next tweezers were used to open the medial longitudinal fissure and, after cutting through the corpus callosum, the diencephalon was separated from the telencephalon bilaterally at the base of the coronal radiations and discarded. Cerebellum, midbrain, and telencephalon were quickly weighed, frozen in liquid nitrogen, and stored in a freezer (−20°C) until assay within two weeks. Each assay compared one brain region from both strains of mice. Tissue from two (telencephalon) or six (midbrain and cerebellum) littermates was pooled for each sample. Of the three regions used for the assays, the midbrain and cerebellum have been shown by lesion studies to play an important role in the expression of AGS in DBA mice [28,29].

To measure [3H]-DHA binding each sample was homogenized with a Brinkman Polytron (setting 6) for 2–5 sec in 30 volumes of ice cold 50 mM Tris-HCl buffer, pH 8.0 The homogenates were centrifuged at 15,000×g for 30 min at 4°C. The supernatants were discarded and the membrane pellets were resuspended in 100 volumes/wet wt tissue of 50 mM Tris-HCl buffer, pH 8.0, containing 0.1% ascorbic acid and 1 μM pargyline.

The assays were performed by a modification of the method of Bylund and Snyder [5]. Incubations (37°C for 30 min) in duplicate were with four different concentrations (0.5–5 nM) [3H]-DHA (New England Nuclear, specific activity: 49.4 Ci/mmole). Nonspecific binding was that determined in the presence of 10 μM (−)-alprenolol. Specific binding was defined as the amount of [3H]-DHA bound in the absence of competing ligand minus the amount bound in the presence of 10 μM (−)-alprenolol. Bound ligand was separated from free by filtration through Whatman GF/B filters presoaked in 100 mM pyrocatechol, followed by two 7 ml cold buffer rinses. Filters were counted in 10 ml Formula 947 (New England Nuclear) with an efficiency of 35%. Total amount of [3H]-DHA bound and K_D's were derived by Scatchard analysis [22] and strain comparisons were made using two-tailed *t*-tests.

RESULTS AND DISCUSSION

Scatchard analysis of the [3H]-DHA binding data revealed that the midbrain of the DBA strain had a significantly greater density of binding sites, expressed as pmoles per gram wet weight tissue, than that of the C57 strain, $t(4)=3.85$, $p<0.02$ (Table 1). There were no strain differences in the density of binding sites for the telencephalon and cerebellum, nor in K_D in any of the three brain regions studied. Since there were no strain differences in protein content per gram tissue in these brain regions, the results would not be changed if the data were normalized to protein content. Thus it appears that, compared with the seizure resistant C57 strain, the AGS susceptible DBA mice have elevated midbrain β-adrenergic receptor densities without a change in receptor affinity as measured by K_D. This increased receptor density could produce an increased neuronal sensitivity to NE in the midbrain of these animals.

TABLE 1

COMPARISON OF [3H]-DIHYDROALPRENOLOL BINDING IN VARIOUS BRAIN REGIONS* IN AGS SUSCEPTIBLE DBA/2 AND NON-SUSCEPTIBLE C57BL/6 MICE

Brain Region	Strain C57	Strain DBA
Midbrain		
Weight (mg)	43 ± 1	36 ± 1†
Bmax (pmoles/g)	0.325 ± 0.07	0.488 ± 0.15‡
Total (fmoles)	13.9 ± 3.3	17.7 ± 5.6
K_D (nM)	0.35 ± 0.09	0.35 ± 0.09
Cerebellum		
Weight (mg)	43 ± 2	36 ± 1†
Bmax (pmoles/g)	0.57 ± 0.02	0.54 ± 0.05
Total (fmoles)	24.4 ± 1.8	19.6 ± 2.1
K_D (nM)	0.11 ± 0.02	0.16 ± 0.04
Telencephalon		
Weight (mg)	225 ± 9	196 ± 4†
Bmax (pmoles/g)	1.87 ± 0.21	1.86 ± 0.30
Total (fmoles)	423 ± 32	374 ± 48
K_D (nM)	0.36 ± 0.05	0.38 ± 0.02

*Each value is the Mean ± S.E.M. of 3–5 separate assays.
†Significantly different from C57 value, $p<0.001$.
‡Significantly different from C57 value, $p<0.02$, *t*-test for related measures.

As has consistently been the case in our laboratory (unpublished observations), all three regions of the DBA mouse brain weighed significantly less than the corresponding regions of the C57 brain, t's≥ 5.82, p's<0.001. Although there was a 50 % greater density of β-adrenergic receptors in the DBA midbrain, because of the lower weight the total number of receptors (expressed as fmoles) was not significantly different from that of the C57 midbrain. In spite of the significantly lower weights the total number of receptors in the DBA cerebellum and telencephalon were also not significantly different from those of the corresponding C57 brain regions.

EXPERIMENT 2: THE EFFECTS OF DL-PROPRANOLOL ON AGS SUSCEPTIBILITY IN DBA/2 MICE

In order to determine if β-adrenergic receptors are related to their seizure activity, dose-effect relationships between the β-adrenergic receptor blocking agent dl-propranolol and AGS were determined in DBA mice at their age of peak susceptibility.

METHOD

Subjects

The subjects were experimentally naive 19–23 day old DBA/2 littermates of both sexes who were bred and reared as in Experiment 1. The animals were weaned on the day of testing.

Drug Treatment

Dl-propranolol HCl (Sigma Chemical Co., St. Louis, MO) was dissolved in normal saline (0.9% NaCl in water, w/v) and the concentration was adjusted so that the different doses were injected in a volume of 0.2 ml/10 g body weight. Littermates were randomly assigned to one of four groups that received IP injections of either 0 (vehicle control), 10, 20, or 40 mg/kg of dl-propranolol HCl (as the salt) 25 minutes before being tested for seizure activity.

Behavioral Testing

An individual animal was placed in a glass jar (20 cm inside diameter × 20 cm deep) with an electric bell built into its cover. The bell produced a broadband noise of 121±1 dB SPL (analyzed with the linear scale of a Bruel and Kjaer Type 2602 measuring amplifier and calibrated microphone at the bottom of the test jar). After the sound stimulus was activated, the onset of each component of the seizure syndrome (wild running, clonic convulsion, and tonic convulsion) was recorded and measured to the nearest sec. If the seizure progressed to the tonic convulsion stage the subject was given artificial respiration in an attempt to prevent death due to anoxia. The stimulus was terminated after 60 sec if no seizure occurred or if seizure activity did not progress to a tonic convulsion.

RESULTS AND DISCUSSION

Dl-propranolol produced a dose-related protection from all stages of the AGS syndrome (Fig. 1).

The DBA mice that received the control injection all showed the wild running stage, and 91% of these progressed to the clonic stage while 85% displayed tonic convulsions. As the dose of dl-propranolol was increased so was the magnitude of its anticonvulsant activity. The 10 mg/kg dose produced a significant decrease in the incidence of both clonic and tonic convulsions, while 20 mg/kg significantly decreased the incidence of wild running, z's$\geq$4.98, p's$<$0.01, test for significant difference between two proportions, two-tailed. The latency for the onset of each component of seizure activity increased with the higher doses of propranolol; however, these results were difficult to analyze because of the small number of animals involved in some instances so the data are not presented. Informal observations indicated that the doses of dl-propranolol used in this study did not produce any general neurotoxicity. There were no overt signs of motor ataxia, movement deficit, or hearing impairment in any of the medicated animals. Even if the mouse did not exhibit wild running it always made some reflex response or attempted to escape from the test chamber at sound onset.

EXPERIMENT 3: THE EFFECTS OF D- AND L-PROPRANOLOL ON AGS SUSCEPTIBILITY IN DBA/2 MICE

In addition to its β-adrenergic blocking activity, propranolol has been shown to have a number of side effects including a membrane-stabilizing local anesthetic-like action related to its ability to block sodium channels [17]. This effect of the drug has been associated with CNS depressant and anticonvulsant activity [11]. Both stereoisomers are equally potent with respect to the membrane stabilizing effect [3], whereas the l-isomer is 10–100 times more potent than the d-isomer with respect to β-receptor blockade [2].

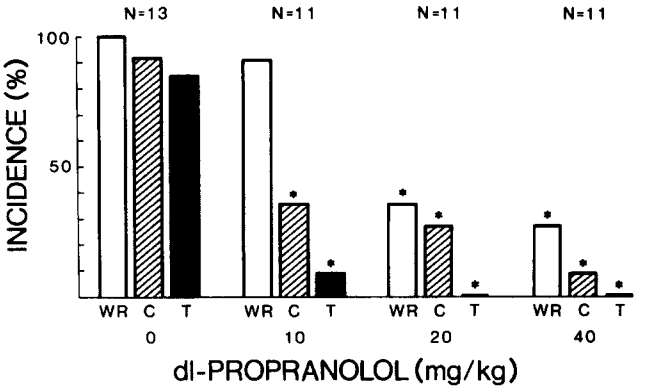

FIG. 1. The effects of increasing doses of dl-propranolol HCl on the percentage of animals exhibiting different components of the audiogenic seizure syndrome in DBA/2 mice. *Indicates that the incidence was significantly lower than that of the saline control group, $p<0.01$, test for significant differences between two proportions, two-tailed. WR=wild running stage, C=clonic convulsion stage, and T=tonic convulsion stage of the syndrome.

Propranolol has also been shown to stereospecifically block serotonin (5-HT) receptors, with the l-isomer being the more potent [18]. Furthermore, there is a preferential uptake of the l-isomer so that at 30 min after injection the ratio of l/d propranolol in the brain is 1.6 [15]. Therefore this experiment compared the effects of specific doses of d- and l-propranolol on AGS susceptibility in DBA mice to determine if propranolol's anticonvulsant activity in the previous experiment was related to its membrane-stabilizing action or receptor blockade.

METHOD

Subjects

The subjects were experimentally naive 19–23 day old DBA/2 littermates of both sexes bred, reared, and weaned as in Experiment 2.

Drug Treatment

Solutions of d- and l-propranolol HCl (Ayerst Laboratories, New York, NY) were prepared and injected as in Experiment 2. This experiment, however, was carried out as two separate experiments. In one, littermates were randomly assigned to either the control condition or the 20 mg/kg dose of d- or l-propranolol, and in the other they were randomly assigned to either the control group, the 10 mg/kg dose of l-propranolol, or the 16 mg/kg dose of d-propranolol. The pretreatment time was again 25 min.

Behavioral Testing Procedure

The same as in Experiment 2.

RESULTS AND DISCUSSION

The control animals from both experiments were pooled into one group that showed 100% incidence of all three stages of the seizure syndrome (Table 2).

Compared to the controls, both doses of d- and of l-propranolol significantly attenuated AGS activity, z's$\geq$4.71, p's$<$0.01, test for significant differences between two proportions, two-tailed. Although 20 mg/kg of

l-propranolol had significantly greater anticonvulsant activity with respect to each stage of the syndrome than the same dose of d-propranolol, z's$\geq$2.34, p's $<$0.02, this does not mean that the results are due to β-receptor blockade. Taking into account the differential uptake of the two isomers into brain at this pretreatment time, the proper comparison is between the 10 mg/kg dose of l-propranolol and the 16 mg/kg dose of d-propranolol. From this comparison it can be seen that there were no differential effects of the two isomers. Because the two isomers are equally potent with respect to the drug's local anesthetic-like action [3], these data suggest that the anticonvulsant effects in both Experiments 2 and 3 of the present study were due to this side effect of propranolol rather than β-adrenergic and/or 5-HT receptor blockade. This conclusion is in agreement with previously published observations on the anticonvulsant activity of d- and l-propranolol in DBA mice [1].

There was a marginally significant (p=0.06) proconvulsant effect on the clonic stage of the syndrome as the dose of d-propranolol was increased from 16 mg/kg to 20 mg/kg. This effect has been reported before in this strain of animals [1] and is possibly related to propranolol's ability to release NE from noradrenergic nerve terminals [26].

EXPERIMENT 4: THE EFFECTS OF DL-PINDOLOL ON AGS SUSCEPTIBILITY IN DBA MICE

With respect to anticonvulsant activity, propranolol's local anesthetic-like action is more potent than beta blockade under the conditions of the present experiments and obviated the possibility of seeing any possible contribution of the latter mechanism of action. Pindolol has been shown to be 3 to 40 times more potent as a β-adrenergic blocking agent than propranolol and 100 to 1000 times less potent with respect to the membrane-stabilizing action [7]. Therefore this experiment studied the effects of various doses of dl-pindolol on AGS susceptibility in DBA mice to see if this beta blocker would have anticonvulsant activity.

METHOD

Subjects

The subjects were of the same origin as in Experiments 2 and 3.

Drug Treatment

Dl-pindolol (Sigma Chemical Company, St. Louis, MO) was injected IP as a suspension in 10% acacia and 0.9% NaCl solution [6]. DBA littermates were randomly assigned to either 0 (vehicle control), 14, 20, 28, or 40 mg/kg dosage conditions, and in this experiment the dose of the drug was varied either by varying concentration or volume. A concentration of 0.5 mg/ml was injected at 0.28 ml/10 g for the 14 mg/kg dose and at 0.40 mg/10 g for the 20 mg/kg dose, whereas a concentration of 1.0 mg/ml was injected at 0.28 ml/10 g for the 28 mg/kg dose and at 0.40 ml/10 g for the 40 mg/kg dose. This was done to conserve drug because pilot studies using acidified solutions of pinolol showed that these solutions were unstable. The suspensions, however, showed no loss of anticonvulsant activity with up to seven days refrigerated storage. The controls all received 0.40 ml/10 g of 10% acacia in normal saline. All subjects were tested 60 min following injection.

TABLE 2

THE EFFECTS OF D- AND L-PROPRANOLOL ON AGS SUSCEPTIBILITY IN DBA/2 MICE

Drug	Dose (mg/kg)	N	Incidence* (%) WR	C	T
Saline Control	—	13	100	100	100
L-Propranolol	10	11	91	27†	18†
	20	13	54†‡	31†‡	0†‡
D-Propranolol	16	11	91	36†	18†
	20	13	100	62†	31†

*WR=wild running attack, C=clonic convulsion, and T=tonic convulsion.
†Significantly different from Saline Control, p's$<$0.01.
‡Significantly different from 20 mg/kg D-Propranolol, p's$<$0.02.

Behavioral Testing Procedure

The same as in Experiments 2 and 3.

RESULTS AND DISCUSSION

Dl-pindolol produced a dose-dependent increase in anticonvulsant activity in about the same dose range as dl-propranolol HCl (Fig. 2).

The lowest dose to significantly attenuate the incidence of tonic convulsions was 14 mg/kg, whereas 20 mg/kg was the lowest dose to significantly reduce the incidence of clonic convulsions and 40 mg/kg was the lowest dose to do the same for the wild running stage of the syndrome, z's$\geq$3.56, p's$<$0.01, test for significant differences between two proportions, two-tailed. As with propranolol, informal observations indicated that these doses of pindolol did not produce any general neurotoxicity. There did not appear to be any motor impairments and even if an animal was completely protected from the seizure it always made some reflex response at sound onset. The results of Experiment 3 indicated that in the present study propranolol's anticonvulsant activity was due to its local anesthetic-like action. Pindolol is at least 100 times less potent than propranolol with respect to this action [7], but in this experiment it protected the DBA mice from audiogenic seizures in about the same systemic dose range as propranolol rather than a dose range approximately 100 times higher which might be expected if its anticonvulsant activity were due to the membrane-stabilizing effect. These results, together with the fact that pindolol is a more potent beta blocker than propranolol, are consistent with the possibility that the protection afforded by pindolol was primarily due to β-adrenergic receptor blockade.

GENERAL DISCUSSION

The results of the present experiments suggest that β-adrenergic receptor mechanisms may be involved in modulating the expression of the genetically programmed audiogenic seizures exhibited by DBA mice. Compared with like-aged seizure resistant C57 animals, [3H]-DHA binding studies showed that the midbrain of DBA mice contains an abnormally high density of β-adrenergic receptors at their age of peak seizure susceptibility. At this same age bilateral electrolytic lesions in the midbrain either attenuate or elimi-

nate AGS activity in these animals [28], suggesting that the proconvulsant action of this region could be mediated by β-adrenergic receptors. In support of this hypothesis, pindolol, a potent β-adrenergic blocking agent, produced dose-dependent anticonvulsant effects on each stage of the AGS syndrome in the present study. Furthermore α-2 adrenergic agonists, that activate autoreceptors on the presynaptic membrane and presumably decrease the amount of NE released into noradrenergic synapses, have been shown to produce anticonvulsant effects in DBA mice [10,13] that can be diminished or reversed by α-2 antagonists [10].

β-Adrenergic blocking agents have been shown to have a number of side effects, the most important of which with respect to anticonvulsant activity is a membrane-stabilizing local anesthetic-like action that produces CNS depression. In fact diphenylhydantoin (phenytoin), a clinically effective anticonvulsant, has this same action [9]. Unlike β-adrenergic receptor blockade, this action is not stereospecific and both the d- and l-isomers of propranolol are equally potent [2]. After taking into account the differential uptake of these two isomers into brain [15], the present study showed that they were equally potent in attenuating AGS in DBA mice. This suggests that propranolol's anticonvulsant activity was due to its local anesthetic-like action in this study, and this is in agreement with the results of an earlier report that used the same mouse strain [1].

Pindolol has been shown to have only very weak membrane-stabilizing effects. It is 0.003 times less potent than propranolol in reducing the spike amplitude of the exposed frog sciatic nerve and at least 0.01 times less potent in the guinea pig cornea test [7]. Although it is impossible to say what the concentrations of these drugs are at the active CNS sites under the conditions of these experiments, pindolol protected DBA mice from AGS in approximately the same systemic dose range as propranolol. Since pindolol's membrane stabilizing activity is at least 100 times less potent than propranolol's, its anticonvulsant effects could be due to β-receptor blockade. In our laboratory 40 mg/kg of pindolol, given systemically, significantly facilitated eating in hungry rats (unpublished observations). Since activation of β-adrenergic receptors in the rat hypothalamus has been shown to inhibit eating [14], this is further support for the suggestion that this systemic dose range of pindolol is producing beta receptor blockade in the CNS.

Both propranolol and pindolol have been shown to block serotonin (5-HT) receptors [18]. Although the possibility that pindolol is working by blocking 5-HT receptors cannot be ruled out, it is unlikely because of evidence indicating that 5-HT is inhibitory to AGS in DBA mice and blocking its receptors should exacerbate seizure activity [4].

The proposed proconvulsant activity of β-adrenergic receptors is difficult to relate to studies which show that increased brain levels of NE attenuate AGS susceptibility in this strain of mice [23] unless one postulates that the overall expression of AGS in these animals is modulated by both α (anticonvulsant)- and β (proconvulsant)-adrenergic receptor mechanisms. In support of this suggestion, α-adrenergic agonists have been shown to produce anticonvulsant effects while β-adrenergic agonists produced proconvulsant effects

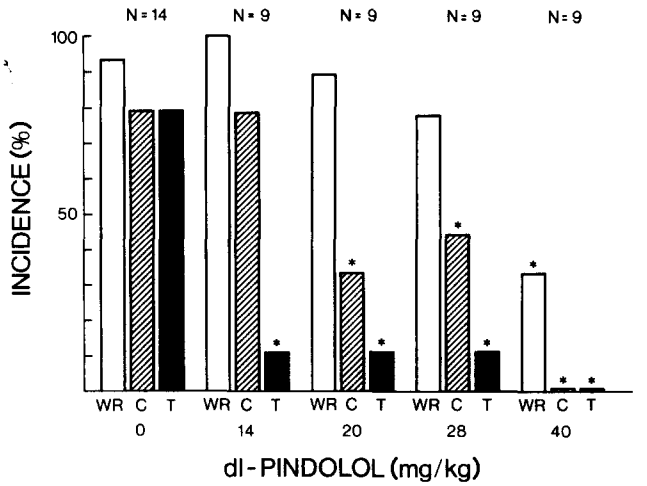

FIG. 2. The effects of increasing doses of dl-pindolol on the percentage of animals exhibiting different components of the audiogenic seizure syndrome in DBA/2 mice. *Indicates that the incidence was significantly lower than that of the vehicle control group, $p<0.01$, test for significant differences between two proportions, two-tailed. WR=wild running stage, C=clonic convulsion stage, and T=tonic convulsion stage of the syndrome.

on rat hippocampal slice preparations [20]. Thus the present findings may generalize to other types of epilepsy.

The increased β-adrenergic receptor density reported here could be the result of an up-regulation secondary to lower midbrain NE levels or it could be genetically predetermined. Although lower endogenous brain levels of NE have been reported in DBA mice at their age of peak seizure susceptibility [13,24], at least two different laboratories have been unable to replicate these findings for whole brain and midbrain ([16], unpublished observations). However, adult levels of β-adrenergic receptors are present in the rat cerebral cortex at two weeks after birth whereas NE stores in the same region develop more slowly and fail to reach adult levels until two months after birth [8]. Together with other evidence [27], this suggests that β-adrenergic receptor densities can be genetically predetermined and do not require an adrenergic input. In an attempt to determine which of these two possible mechanisms could be responsible for the increased receptor density reported here we are currently investigating midbrain NE levels and turnover and beta receptor densities developmentally in these animals using more sensitive assay techniques. We are also attempting to manipulate the receptor densities and to relate any changes to changes in seizure susceptibility.

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