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Effect of norepinephrine release on adrenoceptors in severe seizure genetically epilepsy-prone rats

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Abstract

The genetically epilepsy-prone rat (GEPR) seizure model is characterized by extensive abnormalities in brain noradrenergic function. Earlier studies had suggested that GEPRs might not regulate adrenoceptors in a normal fashion. The purpose of the present study was to determine if GEPR-9s are capable of up and down regulation of α_1- and β-adrenoceptors in response to increments or decrements in extracellular norepinephrine. Seizure induction has been shown to increase extracellular norepinephrine. Chronic sound or electroshock-induced seizures caused down regulation of β-adrenoceptors in frontal cortex and in hippocampus from GEPR-9s. Similarly, chronic daily treatment with the norepinephrine reuptake inhibitor desmethylimipramine produced down regulation of β-adrenoceptors in frontal cortex and in hippocampus from GEPR-9s. As is the case in neurologically normal animals, chronic electroshock-induced seizure did not cause down regulation of β-adrenoceptors in 6-hydroxydopamine pretreated GEPR-9s. Chronic electroshock treatment also caused up-regulation of α_1-adrenoceptors in frontal cortex but not in hippocampus. In 6-hydroxydopamine pretreated GEPR-9s, chronic electroshock treatment caused a further up-regulation of α_1-adrenoceptors in frontal cortex but not in hippocampus. Taken together, these results indicate that GEPR-9s are capable of up and down regulation of α_1- and β-adrenoceptors in a manner that is qualitatively similar to the regulation of these receptors in normal animals. Whether the regulation of brain adrenoceptors is quantitatively different in GEPRs from normal animals remains to be established.

Keywords: GEPR (genetically epilepsy-prone rat); Electroshock; Convulsion; α_1-Adrenoceptor; β-Adrenoceptor; Receptor regulation

1. Introduction

Both strains that make up the genetically epilepsy-prone rat (GEPR) seizure model are characterized by seizure predisposition. In response to a standardized sound stimulus, members of the moderate seizure strain (GEPR-3s) exhibit clonic convulsions while members of the severe seizure strain (GEPR-9s) exhibit tonic–clonic convulsions much like those produced by supramaximal electroshock (Jobe et al., 1973).

Many studies have shown that GEPRs have extensive abnormalities in the major brain inhibitory neurotransmitter systems including norepinephrine, serotonin and GABA (Snead and Miles, 1985; Booker et al., 1986; Roberts and Ribak, 1987; Dailey et al., 1989; Faingold et al., 1989; Lasley, 1991; Lasley and Yan, 1994). Additionally, drugs which decrease noradrenergic or serotonergic transmission increase convulsion intensity in GEPRs while drugs which increase serotonergic or noradrenergic function decrease convulsion intensity in these animals (Dailey et al., 1989; Jobe et al., 1991). Finally, noradrenergic deficiencies exist in GEPRs that have experienced multiple sound-induced seizures, as well as in GEPRs that have been protected from seizure provoking stimuli (Jobe et al., 1986; Dailey et al., 1989, 1991).

Both acute and chronic electroshock have been shown to cause increments in extracellular norepinephrine in non-epileptic rats and in GEPRs (Jobe et al., 1995a,b; Seo et al., 1999). Similarly, both the acute and chronic

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desmethylimipramine increase extracellular norepinephrine by blocking the reuptake of neurotransmitter (Yan et al., 1993a; Seo et al., 1999). Central adrenoceptor systems are also affected by increases in extracellular norepinephrine. Many reports have shown that chronic electroshock seizures cause down regulation of β-adrenoceptors and up-regulation of α_1-adrenoceptors (Bergstrom and Kellar, 1979; Pandey et al., 1979; Kellar and Bergstrom, 1983; Stockmeier et al., 1987; Gleiter and Nutt, 1989). In Addition, Blendy et al. (1991) have reported that electroconvulsive shock increases α_{1b}-, but not α_{1a}-adrenoceptor binding sites in rat cerebral cortex. It has also been reported that chronic desmethylimipramine treatment causes down regulation of β-adrenoceptors (Sarai et al., 1978). Riva and Creese (1989b) have reported that chronic desmethylimipramine treatment decreases β_1-, but not β_2-adrenoceptor binding sites in rat cerebral cortex.

GEPRs are characterized by a lifelong deficiency in presynaptic noradrenergic function. They have lower than normal norepinephrine concentration in virtually all brain areas (Dailey et al., 1991) and they release less norepinephrine in response to drug challenges than do normal animals (Yan et al., 1993b). In the face of these presynaptic deficiencies, one might anticipate that postsynaptic adrenoceptors in GEPR-9 brain might be up regulated in order to compensate for the presynaptic deficiencies. Existing data do not suggest that GEPR brains are characterized by up regulated adrenoceptors (Ko et al., 1984; Nicoletti et al., 1986). The purpose of this present work was to determine if GEPR-9s up and down regulate α_1- and β-adrenoceptors in response to increments and decrements in extracellular norepinephrine. A second purpose was to determine if sound-induced seizures produce β-adrenoceptor changes similar to those produced by electroshock-induced seizures.

2. Materials and methods

2.1. Animals

Animals used in this study were male GEPR-9s and non-epileptic Sprague–Dawley rats weighing 270–320 g. They were obtained from the colonies housed at the University of Illinois College of Medicine at Peoria. Animals were housed at 21 ± 3°C, 40–60% relative humidity and were maintained under 12 h light/12 h dark conditions with ad libitum access to food and water.

2.2. Chemicals and reagents

For the assay of β- and α_1-adrenoceptors, respectively, (−)-[^{3}H]dihydroalprenolol (84.0 Ci/mmol) and 7-methoxy-[^{3}H]prazosin (78.0 Ci/mmol) were obtained from Amersham (Aylesbury, UK). All other chemicals were of reagent grade. Deionized water was used in the preparation of reagents.

2.3. Seizure induction

Electroshock-induced tonic extensor convulsions were induced daily for 12 consecutive days in GEPR-9s. These seizures were induced via an electrical stimulus of 70 mA (60 Hz) administered for 0.5 s through ear-clip electrodes (Swinyard, 1972). This stimulus was obtained from a constant current electroshock seizure apparatus (ME-5300, Metro Scientific, Farmingdale, NY).

In GEPR-9s, tonic extensor sound-induced convulsions were induced daily for 12 consecutive days with 110 dB sound delivered until the onset of convulsion (typically less than 5 s). The acoustical stimulus was produced by two electric bells in a cylindrical metal chamber, 40 cm in diameter by 50 cm high (Jobe et al., 1973).

2.4. Intracerebroventricular injections

For intracerebroventricularly (i.c.v.) injections of 6-hydroxydopamine HCl (Sigma), animals were anesthetized with ketamine and xylazine via intramuscular injection and placed into a stereotaxic frame (David Kopf, USA). A guide cannula (SS, 23 G) was stereotaxically implanted for i.c.v. injections over the right lateral ventricle and attached to the skull with dental acrylic and three skull screws. The coordinates relative to bregma were: AP — 0.8 mm, ML — 1.5 mm (Paxinos and Watson, 1986). The period of postsurgical recovery was at least 5 days. The injection cannula (SS, 30 G) was inserted into the guide cannula and directed into the ventricle with the tip 4.2 mm below the dura by gently restraining awake rats. 6-Hydroxydopamine was dissolved in Ringer's solution (147 mM NaCl, 4 mM KCl, and 2.3 mM $CaCl_2$ in phosphate-buffered solution, pH 7.4) with 0.15% ascorbic acid. The injection solution contained 250 μg of 6-hydroxydopamine per 20 μl. The dose was administered daily for 2 days at the rate of 10 μl/min for 2 min. On the third day, after the last injection of 6-hydroxydopamine, chronic electroshock treatment began. Desmethylimipramine HCl (Sigma) was dissolved in the deionized water and administered by intraperitoneal (i.p.) injection (10 mg/kg, daily for 10 consecutive days).

In our previous data (Seo et al., 1999) and in the preliminary study of this work, vehicle, saline and sham treatments did not change adrenoceptors and the release of norepinephrine either in GEPR-9 or Sprague–Dawley rats. Therefore, we used GEPR-9 control as a control group representing sham, saline and vehicle treated-GEPR-9 control group to minimize the number of animals to be sacrificed.

2.5. Norepinephrine concentrations and protein concentrations

In order to confirm that the 6-hydroxydopamine treatments depleted norepinephrine, concentrations of nor-

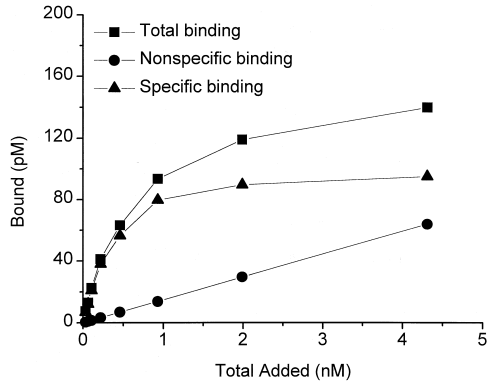

Fig. 1. The saturation curve of [^{3}H]dihydroalprenolol binding data showing total, specific and nonspecific binding as a function of free ligand concentration. Binding was measured over a [^{3}H]dihydroalprenolol concentration range of 0.06–6.20 nM. This experiment was replicated more than three times (see Table 1 for B_{max} and K_d values of each treated group). LIGAND program still analyzed the total binding data as a single saturable binding site with the same B_{max} and K_d as were determined with saturation curves when the highest concentration of [^{3}H]dihydroalprenolol was 6 nM (Riva and Creese, 1989a). Therefore, we employed the concentration of [^{3}H]dihydroalprenolol for the total binding of β-adrenoceptors under 6 nM to exclude binding of [^{3}H]dihydroalprenolol to serotonin receptors.

epinephrine were measured bilaterally in the entire hippocampus and bilaterally in the entire frontal cortex using high performance liquid chromatography (HPLC) with electrochemical detection as previously described (Dailey et al., 1991).

Protein was determined according to the method of Bradford (1976) using bovine serum albumin as a standard.

2.6. β-Adrenoceptor binding assay

For the assay of β-adrenoceptors, tissues were homogenized in buffer solution (50 mM Trizma base, 5 mM EDTA, 100 mM NaCl, pH 8.0; 50 × tissue volume) using the Tekmar Tissumizer (Cincinnati, OH) set at 7 for 20 s. The homogenates were centrifuged at 40,000 × g for 10 min at 4°C. The centrifugation process was repeated two additional times. The final tissue pellets were re-suspended in fresh buffer (w/v, 1:50 for frontal cortex, 1:62.5 for hippocampus). β-Adrenoceptor binding sites were measured in aliquots of tissue equivalent to 10 mg frontal cortex and 8 mg hippocampus. Tissues were incubated in triplicate for 30 min at 25°C with [^{3}H]dihydroalprenolol (0.06–6.20 nM). The total incubation volume was 0.52 ml and the nonspecific binding was floated and calculated by LIGAND program (Riva and Creese, 1989a). [^{3}H]Dihydroalprenolol bound to the membrane was separated by rapid filtration through a 0.3% polyethylenimine presoaked Whatman GF/B filter and washed three times with 5 ml ice-cold 50 mM Tris buffer, using a modified Brandel cell harvester (Gaithersburg, MD). Each filter was placed in a counting vial to which 10 ml of scintillation cocktail was added and counted in a liquid scintillation counter. The binding data were analyzed using the iterative curve-fitting program LIGAND (Munson and Rodbard, 1980).

[^{3}H]Dihydroalprenolol was reported not to be a satisfactory ligand for the characterization of β-adrenoceptors if nonspecific binding is defined using classical agonists or antagonists. Riva and Creese (1989a) have reported that [^{3}H]dihydroalprenolol can be used to quantify β-adrenoceptors if its total binding is analyzed by the computer program LIGAND or if selective β-adrenoceptor antagonists are used to define nonspecific binding. Therefore, all saturation data for [^{3}H]dihydroalprenolol binding to β-adrenoceptors in the present study were analyzed by fitting the total binding for [^{3}H]dihydroalprenolol with the nonspecific allowed to float and being fitted by the program as a linear function of ^{3}H-ligand concentration.

2.7. α_1-Adrenoceptor binding assay

For the assay of α_1-adrenoceptors, tissues were homogenized in buffer solution (50 mM Trizma base, 5 mM EGTA, 10 mM $MgCl_2$, pH 7.6; 50 × tissue volume) and

Table 1
β-Adrenoceptors of GEPR-9s: [^{3}H]dihydroalprenolol binding[a]

Treatment regimen	Frontal cortex		Hippocampus	
	B_{max} (fmol/mg protein)	K_d (nM)	B_{max} (fmol/mg protein)	K_d (nM)
Sprague–Dawley control	94.83 ± 1.67 (5)	0.33 ± 0.01 (5)	51.79 ± 0.81 (5)	0.49 ± 0.01 (5)
GEPR-9 control	96.10 ± 0.56 (5)	0.35 ± 0.01 (5)	55.83 ± 1.47 (5)	0.48 ± 0.01 (5)
GEPR-9 electroshock	76.64 ± 3.28 (5)[b]	0.33 ± 0.01 (5)	40.29 ± 2.21 (5)[b]	0.48 ± 0.02 (5)
GEPR-9 sound	79.03 ± 2.57 (5)[b]	0.37 ± 0.01 (5)	46.42 ± 1.55 (5)[b]	0.49 ± 0.02 (5)
GEPR-9 desmethylimipramine	70.87 ± 1.17 (5)[b]	0.36 ± 0.01 (5)	27.20 ± 1.25 (5)[b]	0.49 ± 0.02 (5)
GEPR-9 6-hydroxydopamine + sham	142.14 ± 2.73 (4)[c]	0.48 ± 0.02 (4)	109.10 ± 2.26 (3)[c]	0.60 ± 0.01 (3)
GEPR-9 6-hydroxydopamine + electroshock	138.63 ± 3.34 (4)[c]	0.48 ± 0.01 (4)	105.06 ± 3.80 (3)[c]	0.58 ± 0.02 (3)

[a] Each numerical values in a single cell of the table represents the mean ± SEM (N).
[b] Indicates a significant difference ($P < 0.01$) from the GEPR-9 control or sham group within the same set.
[c] Indicates a significant difference ($P < 0.01$) from the GEPR-9 control group.

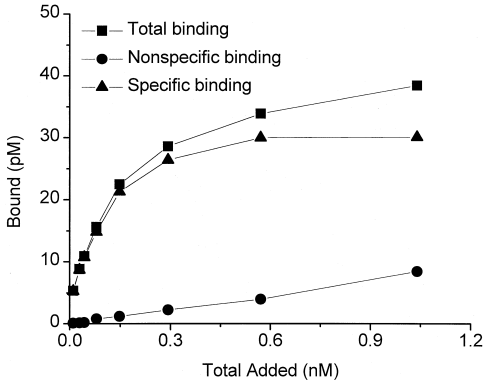

Fig. 2. The saturation curve of [^{3}H]prazosin binding data showing total, specific and nonspecific binding as a function of free ligand concentration. Binding was measured over a [^{3}H]prazosin concentration range of 0.003–1.20 nM. This experiment was replicated more than four times (see Table 2 for B_{max} and K_d values of each treated group).

centrifuged as described above for β-adrenoceptors. The final tissue pellets were re-suspended in fresh buffer (w/v, 1:200 for frontal cortex, 1:125 for hippocampus). α_1-Adrenoceptor binding sites were measured in aliquots of tissue equivalent to 5 mg frontal cortex and 8 mg hippocampus. Tissues were incubated in duplicate for 30 min at 25°C with [^{3}H]prazosin (0.003–1.20 nM). Total incubation volume was 2.0 ml and 1.0 μM phentolamine was used for nonspecific binding. [^{3}H]Prazosin bound to the membrane was separated by rapid filtration through a 0.3% polyethylenimine presoaked Whatman GF/B filter and washed three times with 5 ml ice-cold 10 mM Tris buffer, using a modified Brandel cell harvester (Gaithersburg, MD). Each filter was placed in a counting vial to which 10 ml of scintillation cocktail was added and counted in a liquid scintillation counter. The binding data were analyzed using the iterative curve-fitting program LIGAND (Munson and Rodbard, 1980).

2.8. Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) followed by Newman–Keuls' test. Each value was expressed as the mean ± SEM and statistical significance was accepted for $P < 0.01$ or $P < 0.05$.

3. Results

3.1. β-Adrenoceptor density

Fig. 1 shows an example of saturation curve of [^{3}H]dihydroalprenolol binding data. The β-adrenoceptor densities (B_{max}) and apparent dissociation constants (K_d) for GEPR-9s are summarized in Table 1. The B_{max} and K_d values for dihydroalprenolol binding in untreated GEPR-9 frontal cortex and hippocampus were not different from those found in untreated Sprague–Dawley rats. Chronic electroshock convulsions and chronic sound-induced convulsions significantly decreased the B_{max} for dihydroalprenolol binding in frontal cortex and hippocampus ($P < 0.01$). Chronic desmethylimipramine treatment also significantly decreased the B_{max} for dihydroalprenolol binding in the frontal cortex and hippocampus ($P < 0.01$).

6-Hydroxydopamine caused more than a 90% depletion of norepinephrine in the hippocampus and frontal cortex. This depletion caused a statistically significant increase in the B_{max} for dihydroalprenolol binding in the frontal cortex (by 48%) and in the hippocampus (by 95%) ($P < 0.01$ in both cases). In the 6-hydroxydopamine pretreated animals, however, chronic electroshock convulsions failed to decrease the B_{max} for dihydroalprenolol binding either in the frontal cortex or in the hippocampus. No significant K_d differences were detected in either brain region in any treatment group.

3.2. α_1-Adrenoceptor density

Fig. 2 shows an example of saturation curve of [^{3}H]prazosin binding data. The α_1-adrenoceptor densities (B_{max}) and apparent dissociation constant (K_d) for GEPR-9s are summarized in Table 2. Chronic electroshock convulsions significantly increased the B_{max} for prazosin binding in the frontal cortex ($P < 0.01$), however, in the hippocampus, the B_{max} was not changed.

6-Hydroxydopamine treatment caused a significant increase in the B_{max} for prazosin binding in the frontal cortex (by 61%) and in the hippocampus (by 19%) ($P < 0.01$ in both cases). In the 6-hydroxydopamine pretreated

Table 2
α_1-Adrenoceptors of GEPR-9s: [^{3}H]prazosin binding[a]

Treatment regimen	Frontal cortex		Hippocampus	
	B_{max} (fmol/mg protein)	K_d (nM)	B_{max} (fmol/mg protein)	K_d (nM)
GEPR-9 sham	218.57 ± 2.60 (5)	0.0566 ± 0.0042 (5)	105.59 ± 2.04 (5)	0.0988 ± 0.0055 (5)
GEPR-9 electroshock	273.35 ± 5.42 (5)[b]	0.0507 ± 0.0037 (5)	101.29 ± 1.41 (4)	0.0975 ± 0.0042 (4)
GEPR-9 6-hydroxydopamine + sham	352.93 ± 4.72 (5)[c]	0.0472 ± 0.0017 (5)	125.12 ± 3.66 (4)[c]	0.0798 ± 0.0029 (4)
GEPR-9 6-hydroxydopamine + electroshock	496.07 ± 13.15 (5)[b,c]	0.0447 ± 0.0026 (5)	127.90 ± 3.51 (4)[c]	0.0829 ± 0.0060 (4)

[a] Each numerical value in a single cell of the table represents the mean ± SEM (N).
[b] Indicates a significant difference ($P < 0.01$) from the sham group within the same set.
[c] Indicates a significant difference ($P < 0.01$) from the sham group.

animals, chronic electroshock significantly ($P < 0.01$) increased the B_{max} for prazosin binding in the frontal cortex ($P < 0.01$), but in the hippocampus, the B_{max} was not changed. No significant K_d differences were detected in either brain region in any of the treatment groups.

4. Discussion

Our current observations show that chronic electroshock convulsions and chronic sound-induced convulsions both decrease β-adrenoceptor B_{max} in the frontal cortex and hippocampus of GEPR-9s. Consistent with these are the previous findings that β-adrenoceptor binding decreased after the last stimulation of fully kindled animals (McIntyre and Roberts, 1983; Michelson and Buterbaugh, 1987). Thus, the seizure-induced change in adrenoceptor density appears to be independent of the seizure provoking modality. This result suggests that it is the seizure per se that brings about the brain chemistry changes that lead to adrenoceptor alterations.

Previous studies have shown that electroshock produces elevations in extracellular norepinephrine in the hippocampus and frontal cortex of anesthetized rats (Glue et al., 1990; Thomas et al., 1992) and in conscious freely-behaving rats (Seo et al., 1999). These studies also showed that pretreatment of Sprague–Dawley rats with 6-hydroxydopamine reduced norepinephrine extracellular levels so that they were below detection limits (Seo et al., 1999). We showed previously that depletion of norepinephrine either by interference with neurotransmitter storage by reserpine or destruction of noradrenergic neurons with 6-hydroxydopamine prevented the electroshock-induced down regulation of β-adrenoceptors in Sprague–Dawley rats. In the present experiments, 6–hydroxydopamine pretreatment prevented electroshock-induced β-adrenoceptor down regulation in GEPR-9s. Desmethylimipramine has been extensively studied as a norepinephrine uptake inhibitor. The drug increases the concentration of extracellular norepinephrine by inhibiting the norepinephrine transporter (Yan et al., 1993a; Seo et al., 1999). Our chronic desmethylimipramine regimen in GEPR-9s produced substantial decrements in β-adrenoceptor B_{max} in both the frontal cortex and hippocampus, an effect which is consistent with the previous observations in Sprague–Dawley rats (Sarai et al., 1978; Riva and Creese, 1989b). These data support the concept that down regulation of β-adrenoceptors is mediated through increments in extracellular norepinephrine. Thus, in this regard, GEPR-9s appear to regulate β-adrenoceptors in a manner that is at least qualitatively similar to Sprague–Dawley rats.

Electroshock induced an increase in B_{max} for prazosin binding in the frontal cortex of GEPR-9 rats. This increase in α_1-adrenoceptors was not prevented by the neuronal destruction produced by the 6-hydroxydopamine pretreatment. Thus, because 6-hydroxydopamine causes destruction and atrophy of noradrenergic nerve terminals, the data suggest that the signal for the up-regulation is derived neither from the norepinephrine release nor from the release of other chemicals from noradrenergic processes or terminals. A similar conclusion was reached by Blendy et al. (1991) who suggested that electroshock convulsions might affect the transcription, translation, post-translational processing or turnover of α_1-adrenoceptor through processes that are independent of any effects on noradrenergic neurons.

Electroshock induced an increase in B_{max} for prazosin binding in GEPR-9 frontal cortex but not in hippocampus. The data suggest that electroshock affects α_1-adrenoceptors in a discrete anatomical region. While the effects of electroshock on α_1-adrenoceptor binding are anatomically limited to specific brain structures, it is not known what functional role these areas serve in relation to the etiology of seizures in GEPRs.

In summary, the present data show that chronic sound-induced seizures in GEPR-9s produce a down regulation of β-adrenoceptors, which is qualitatively and quantitatively similar to the down regulation of β-adrenoceptors produced by chronic electroshock-induced seizures in these animals. Additionally, the data in the literature coupled with the present results indicate that GEPR-9s can up and down regulate α_1- and β-adrenoceptors in a qualitatively normal fashion. Whether regulation of these receptors in GEPRs is quantitatively abnormal enough to be of etiological importance for seizure manifestation remains to be established.

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