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Further evidence of anticonvulsant role for 5-hydroxytryptamine in genetically epilepsy-prone rats

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1 This study was designed to evaluate further the role of 5-hydroxytryptamine (5-HT) in regulating susceptibility and/or intensity of audiogenic seizures in genetically epilepsy-prone rats.

2 The effects of sertraline, a highly selective and potent inhibitor of 5-HT uptake, on both the intensity of the audiogenic seizures and the extracellular concentrations of 5-HT in the thalamus were evaluated in severe seizure genetically epilepsy-prone rats.

3 Sertraline (7.5, 15 and 30 mg kg^{-1}, i.p.) produced a dose-dependent reduction in the intensity of the audiogenic seizures.

4 Brain microdialysis studies showed that the same doses of sertraline also caused dose-dependent increases in the extracellular 5-HT concentration in the thalamus of the freely moving rats.

5 The peak anticonvulsant effect correlated temporally with the peak increases in the extracellular 5-HT concentration for this drug.

6 It is concluded that enhancement of 5-hydroxytryptaminergic transmission may contribute to the anticonvulsant effect of sertraline in severe seizure genetically epilepsy-prone rats.

7 The present results coupled with earlier investigations support the hypothesis that 5-HT plays an anticonvulsant role in genetically epilepsy-prone rats.

Keywords: Sertraline; 5-hydroxytryptamine; microdialysis; anticonvulsant effect; genetically epilepsy-prone rats (GEPRs)

Introduction

Previous reports from this laboratory indicate that fluoxetine, a selective 5-hydroxytryptamine (5-HT) uptake inhibitor, has anticonvulsant effects in genetically epilepsy-prone rats (GEPRs) (Dailey *et al.*, 1992a,b; Yan *et al.*, 1994a,b). Also, the protection against audiogenic seizure following the administration of fluoxetine appears to be selectively correlated with enhanced 5-hydroxytryptaminergic transmission (Dailey *et al.*, 1992a,b; Yan *et al.*, 1994a,b). An important question raised by these findings is whether the anticonvulsant action following the administration of the 5-HT uptake inhibitor in GEPRs is peculiar to fluoxetine. This study was designed to evaluate further the role of 5-HT in regulating susceptibility and/or severity of audiogenic seizures in GEPRs. For this purpose, sertraline, another highly selective and potent inhibitor of 5-HT uptake (Koe *et al.*, 1983; Heym & Koe, 1988), was studied. In this work, we assessed the effects of sertraline on the intensity of the audiogenic seizure in GEPRs. In addition, the influence of the drug on the 5-hydroxytryptaminergic transmission was investigated by measuring 5-HT content in brain extracellular fluid by intracerebral microdialysis. The extracellular 5-HT accumulations were measured in the thalamus of the freely moving GEPRs. The reasons for which the thalamus was selected are as follows: (1) Previous studies from this laboratory showed that the thalamus has equal 5-hydroxytryptaminergic deficits in moderate seizure GEPRs (GEPR-3s) and severe seizure GEPRs (GEPR-9s), and may be a candidate for regulation of seizure susceptibility in the GEPRs (Dailey *et al.*, 1992a). (2) The thalamus is a representative of 5-hydroxytryptaminergic terminals in the forebrain receiving ascending raphe nuclei innervation (Jacobs & Azmitia, 1992).

Methods

Animals

Male GEPR-9s weighing 280-350 g were used as experimental subjects. They were obtained from the resource colony housed at the University of Illinois College of Medicine at Peoria. This strain of GEPRs exhibits a generalized tonic extensor convulsion with or without the prior appearance of a running episode in response to standard sound stimulation.

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 before use.

Seizure induction and evaluation

Audiogenic seizures were induced and evaluated according to our standard protocol (Jobe *et al.*, 1973). Animals were placed individually in a cylindrical chamber and the sound stimulus was initiated within 15 s. A sound level of approximately 115 db relative to 2×10^{-4} dyne cm^{-2} was generated by two electric bells mounted in the chamber lid. The stimulus was continued until the animal convulsed or for a maximum of 90 s.

The audiogenic response score (ARS) developed by Jobe *et al.* (1973) was used to evaluate convulsion intensity. As shown in Figure 1, the ARS is an ordinal rating scale from 0 to 9 in which increasing numerical scores denote increasingly severe seizures. All the assessments of seizure scores were performed by one observer who was unaware of experimental treatments.

Microdialysis

The animals were prepared for the microdialysis experiments as described by Yan *et al.* (1992). In brief, surgery was conducted on a Kopf stereotaxic instrument under anaesthesia with a combination of sodium pentobarbitone (35 mg kg^{-1}, i.p.) and halothane (5% in oxygen). A dialysis guide cannula (Harvard Apparatus, Inc., S. Natick, MA., U.S.A.) was stereotaxically implanted over the thalamus and attached to the skull with dental acrylic and machine screws. The coordinates relative to bregma were: AP -3.6 mm, L 2.4 mm (Paxinos & Watson, 1986). The period of post-surgical recovery was at least 5 days. On the experimental day, a loop dialysis probe (3 mm in length) was inserted into the guide and directed to the

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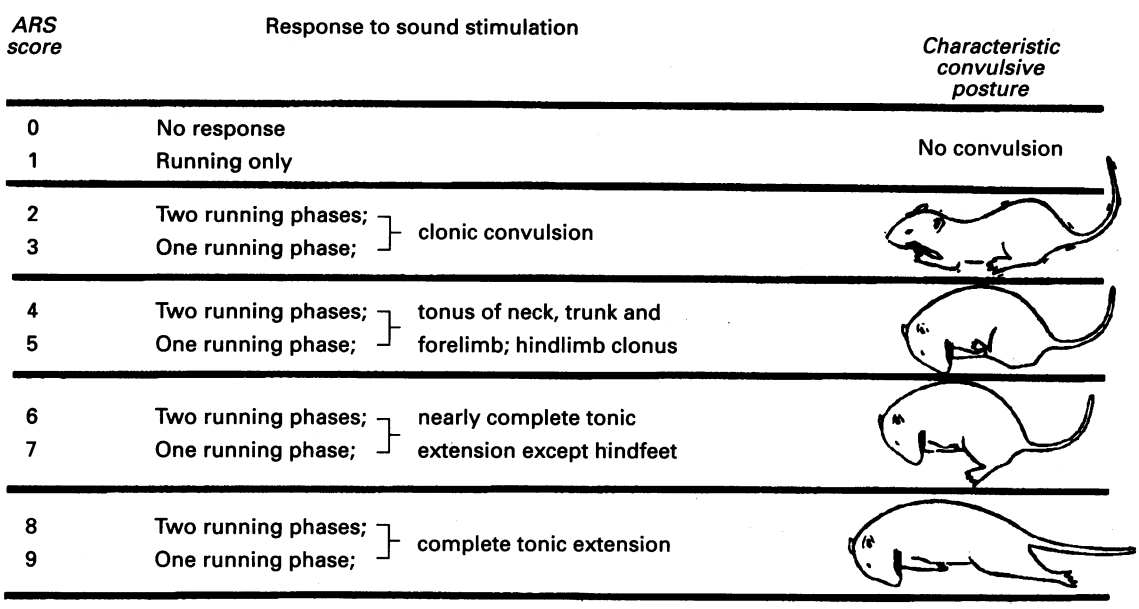

Figure 1 Diagrammatic depiction of the audiogenic response score (ARS) system for evaluation of the intensity of sound-induced convulsions in the genetically epilepsy-prone rats (GEPRs). Taken with permission from Dailey & Jobe (1985).

thalamus with the tip 6.6 mm below the dura while gently restraining awake rats. The animals were then placed individually in a plexiglass chamber where they could move about freely. Artificial cerebrospinal fluid (pH 7.25–7.35), which contained (g l^{-1}); NaCl 8.66, KCl 0.224, $CaCl_2 2H_2O$ 0.206, $MgCl_2 6H_2O$ 0.163, $Na_2HPO_4H_2O$ 0.214 and $NaH_2PO_4H_2O$ 0.027, was perfused at 0.6 μl min^{-1}. Consecutive samples were collected throughout 60 min intervals. Samples were stabilized with 800 pmol of L-cysteine dissolved in 5 μl of 0.1 N HCl. No treatments were administered until basal release of 5-HT was stable. This occurred typically 4–5 h after probe implantation. Vehicle (dimethyl sulphoxide) or sertraline (7.5, 15 and 30 mg kg^{-1}, free base weight, the same below) was administered intraperitoneally after two to three basal release measures were made. Dialysis was continued for 8 h thereafter.

Analytical procedure

Dialysates were assayed for 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) by high performance liquid chromatography (h.p.l.c.) with electrochemical detection. The h.p.l.c. system consisted of a Water Associates pump (Model 510) and a 15 cm × 2 mm column supplied by Phenomenex (3 μm particle ODS-20 packing). Electrochemical detection was accomplished with a LC4B detector (BAS Inc., W. Lafayette, IN., U.S.A.), maintained at +0.70 V with respect to an Ag/AgCl reference electrode. Output was recorded on a Shimadzu C-R6A integrator. The mobile phase consisted of a 0.1 M citrate-phosphate buffer (pH 3.80–3.85) containing EDTA-2Na (10 μM), octyl sodium sulphate (150 mg l^{-1}) and a final concentration of 15% methanol. A flow rate of 0.4 ml min^{-1} was used throughout. The retention times and limits of detection for 5-HT and 5-HIAA were 8.4 min, 20 fmol and 4.7 min, 20 fmol, respectively.

After completion of the dialysis, the animals were decapitated and the brains immersion-fixed overnight in buffered 4% paraformaldehyde. Coronal sections (40 μm thick) were cut on a freezing microtome, stained with neutral red and analyzed in the light microscope. The locations of the dialysis probes were verified in each brain.

Experimental design

Prior to use, each GEPR-9 was subjected to sound stimulation three times at weekly intervals in order to ensure an ARS of 9 for each subject. Previous studies have shown that after GEPR-9s have experienced three audiogenic seizures, there is a very high probability (95% or more) that on subsequent sound stimulation they will exhibit complete tonic convulsions (Dailey & Jobe 1985; Mishra *et al.*, 1988). Then, the animals were divided into two groups. The first group (48 rats) was used to test the effects of sertraline on the intensity of the audiogenic seizure. In this group, sertraline (7.5, 15 and 30 mg kg^{-1}) or vehicle was administered i.p., respectively, to four groups of 12 animals which were thereafter sound stimulated hourly. The second group (28 rats) was used for microdialysis studies.

Drugs

Sertraline hydrochloride (Pfizer, Groton, CT., U.S.A.) was dissolved in dimethyl sulphoxide (Sigma, St. Louis, MO., U.S.A.) and was administered i.p. in a volume of 1 ml kg^{-1}.

Analysis of data

Effects of sertraline on ARSs were analyzed through the use of one-way analysis of variance (ANOVA), followed by the Duncan Multiple Range Test. Changes in extracellular 5-HT and 5-HIAA levels induced by administration of sertraline or vehicle were expressed as percentage of the mean of the absolute amounts detected in two samples collected consecutively just before drug injection. ANOVA followed by the Duncan Multiple Range Test were used for comparisons among the different treatment groups at a given time interval after drug administration. When performing analysis of the correlation between the means of extracellular 5-HT concentrations in the thalamus and the means of ARS in GEPR-9s treated with sertraline, the means of ARS were obtained from the experiments in which the effects of the drug on the intensity of the audiogenic seizure were tested. The means of extracellular 5-HT concentrations, which were expressed as fmol μl^{-1} of dialysate, were obtained from the corresponding microdialysis experiments.

Results

Effects of sertraline on the intensity of the audiogenic seizure in GEPR-9s

As shown in Table 1, administration of vehicle did not decrease the intensity of the audiogenic seizure and no reduction

Table 1 Effects of sertraline on the intensity of the audiogenic seizure in GEPR-9s

Dose (mg kg^{-1})	*Audiogenic response score (ARS) after treatment*						
	1 h	*2 h*	*3 h*	*4 h*	*5 h*	*8 h*	*24 h*
0	9.00±0.00	9.00±0.00	9.00±0.00	9.00±0.00	9.00±0.00	9.00±0.00	9.00±0.00
7.5	9.00±0.00	9.00±0.00	8.50±0.50	8.50±0.50	7.50±0.82	8.00±0.72	9.00±0.00
15	9.00±0.00	7.67±0.62^{ab}	6.50±0.70^{ab}	6.67±0.73^{ab}	6.83±0.58^{a}	5.58±0.84^{ab}	9.00±0.00
30	7.67±0.71^{abc}	6.08±0.95^{ab}	4.58±0.73^{abc}	3.25±0.72^{abc}	3.67±0.67^{abc}	2.83±0.51^{abc}	7.50±1.01

Sertraline (7.5, 15 and 30 mg kg^{-1}) or vehicle was administered i.p. to four groups of 12 animals which were therafter sound stimulated at the times shown in the table. Values are mean±s.e.mean.
$^{a}P<0.05$ compared with vehicle group; $^{b}P<0.05$ compared with 7.5 mg kg^{-1} group; $^{c}P<0.05$ compared with 15 mg kg^{-1} group. ANOVA (one way) followed by Duncan Multiple Range Test.

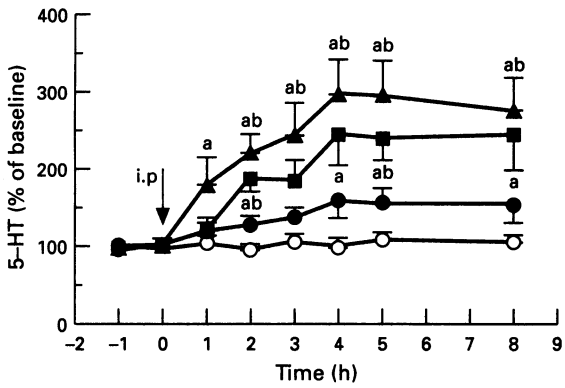

Figure 2 Effects of sertraline on extracellular 5-hydroxytryptamine (5-HT) levels in the thalamus of GEPR-9s. Sertraline 7.5 (●), 15 (■) and 30 mg kg^{-1} (▲) or vehicle (○) was injected i.p. at the time indicated by the arrow. 5-HT data are expressed as the percentage of the mean baseline. Mean±s.e.mean values from 7 animals are shown. The mean basal outputs of 5-HT (fmol μl^{-1} of dialysates±s.e.mean [*n*]) for vehcile, 7.5 mg kg^{-1}, 15 mg kg^{-1} and 30 mg kg^{-1} groups are: 1.08±0.08 [*n*=14], 1.02±0.10 [*n*=14], 0.93±0.06 [*n*=14] and 1.09±0.06 [*n*=14], respectively. Statistical assessments show that the basal 5-HT levels do not differ significantly among the groups of animals. $^{a}P<0.05$ compared with vehicle group. $^{b}P<0.05$ compared with 7.5 mg kg^{-1} group. ANOVA (one way) followed by Duncan Multiple Range Test.

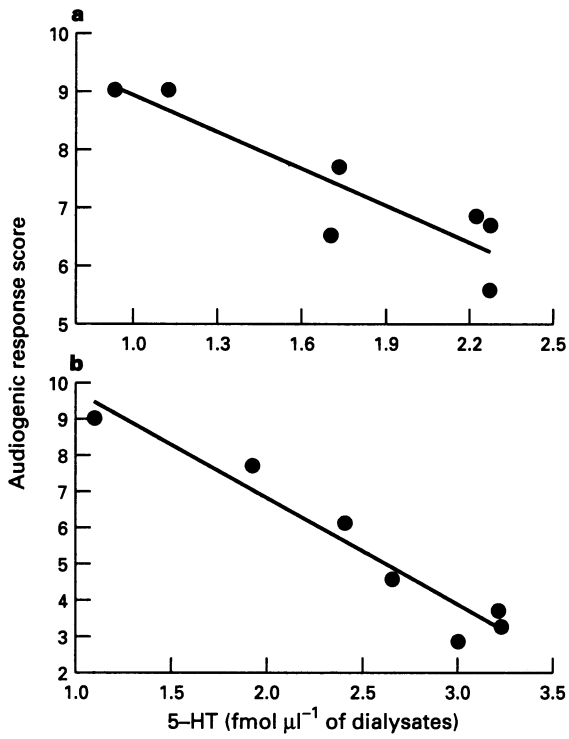

Figure 3 Correlation between means of extracellular 5-hydroxytryptamine (5-HT) concentrations in the thalamus and means of audiogenic response scores (ARSs) in GEPR-9s treated with sertraline at either 15 mg kg^{-1} (a) or 30 mg kg^{-1} (b). The means of ARSs were obtained from the corresponding experiments in which the time course of the anti-convulsant effect was determined. The means of extracellular 5-HT concentrations were obtained from the corresponding microdialysis experiments. Each point represents both the mean of ARSs (*n*=12) and the mean of extracellular 5-HT concentrations (*n*=7) at 0, 1, 2, 3, 4, 5, 8 h after administration of sertraline. 5-HT data are expressed as fmol μl^{-1} of dialysates. The correlation coefficient Γ is 0.899 ($P<0.01$) for 15 mg kg^{-1} and 0.967 ($P<0.001$) for 30 mg kg^{-1}. The regression equations are ARS=−2.11×5-HT+11.01 (15 mg kg^{-1}) and ARS=−2.93×5-HT+12.61, respectively.

in the ARS was observed. Intraperitoneal injection of sertraline (7.5, 15, and 30 mg kg^{-1}) produced a dose-dependent reduction in the seizure intensity. The peak anticonvulsant effects appeared at the 5th to the 8th hour after the drug administration. At the 8th hour after systemic administration of sertraline, the ARS still remained low and no tendency toward a recovery was observed in either the 15 mg kg^{-1} or 30 mg kg^{-1} dose group.

Effects of sertraline on extracellular 5-HT concentrations in the thalamus of GEPR-9s

Prior to the treatment, the mean 5-HT concentrations (fmol μl^{-1} of dialysate±s.e.mean) in thalamic extracellular fluid in 4 experimental groups of GEPR-9s were: 1.08±0.08 (vehicle, *n*=14); 1.02±0.10 (7.5 mg kg^{-1}, *n*=14); 0.93±0.06 (15 mg kg^{-1}, *n*=14); and 1.09±0.06 (30 mg kg^{-1}, *n*=14). Statistical assessments show that the basal 5-HT levels do not differ significantly among the groups of animals. As can be seen from Figure 2, administration of vehicle produced no statistically significant increases in extracellular 5-HT concentrations. There was a tendency toward an increase in extracellular 5-HT concentrations after injection of 7.5 mg kg^{-1} of sertraline, although the effect was not statistically significant. Systemic administrations of sertraline (15 and 30 mg kg^{-1}) produced statistically significant increases in 5-HT contents. These elevations became apparent in the dialysis samples completed 1–2 h following the injection of the drug and reached the maximum levels (244% and 296% of baseline for 15 and 30 mg kg^{-1}, respectively) in approximately 4 h. From this point, an almost equally high plateau was maintained for the remainder of the 8 h interval of observation. At the 8th hour after sertraline administration, the extracellular 5-HT concentrations remained 243% and 275% of pre-injection baseline for 15 and 30 mg kg^{-1}, respectively. Comparing the time courses of the increase in extracellular 5-HT (Figure 2) with those of the anticonvulsant effect (Table 1), we found that the maximum plateau of extracellular 5-HT levels after treatment with sertraline at both doses (15 and 30 mg kg^{-1}) corresponds temporally with the peak anticonvulsant effects.

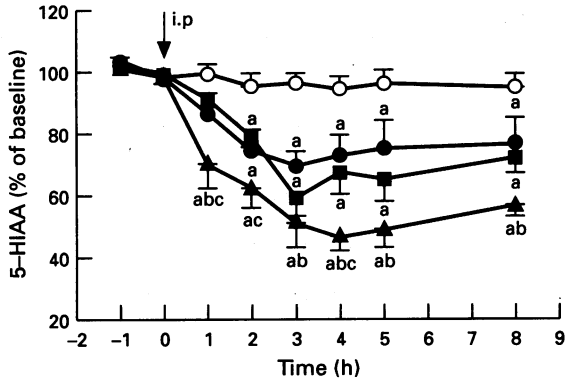

Figure 4 Effects of sertraline on extracellular 5-hydroxyindoleacetic acid (5-HIAA) levels in the thalamus of GEPR-9s. Sertraline 7.5 (●), 15 (■) and 30 mg kg^{-1} (▲) or vehicle (○) was injected i.p. at the time indicated by the arrow. 5-HIAA data are expressed as the percentage of the mean baseline. Mean ± s.e.mean values from 7 animals are shown. The mean basal outputs of 5-HIAA (fmol μl^{-1} of dialysates ± s.e.mean [n]) for vehicle, 7.5 mg kg^{-1}, 15 mg kg^{-1} and 30 mg kg^{-1} groups are: 581.9 ± 38.9 [n = 14], 609.3 ± 41.2 [n = 14], 550.9 ± 46.2 [n = 14] and 512.9 ± 36.1 [n = 14], respectively. Statistical assessments show that the basal 5-HIAA levels do not differ significantly among the groups of animals. $^{a}P < 0.05$ compared with vehicle group. $^{b}P < 0.05$ compared with 7.5 mg kg^{-1} group. $^{c}P < 0.05$ compared with 15 mg kg^{-1} group. ANOVA (one way) followed by Duncan Multiple Range Test.

Relationship between extracellular 5-HT concentration and ARS for sertraline

As can be seen in Figure 3, a negative correlation exists between extracellular 5-HT concentration and audiogenic seizure intensity for both 15 and 30 mg kg^{-1} of sertraline. Statistical analysis of the regression lines showed that the correlation coefficients (Γ) are 0.899 (15 mg kg^{-1}, $P < 0.01$, a) and 0.967 (30 mg kg^{-1}, $P < 0.001$, b), respectively. The slopes of the regression line for 15 and 30 mg kg^{-1} are −2.11 and −2.93, respectively; and not statistically different from each other ($P > 0.1$).

Effects of sertraline on extracellular 5-HIAA concentrations in the thalamus of GEPR-9s

Prior to the treatment, the mean 5-HIAA concentrations (fmol μl^{-1} of dialysate ± s.e.mean) in thalamic extracellular fluid in 4 experimental groups of GEPR-9s were: 581.9 ± 38.9 (vehicle, n = 14); 609.3 ± 41.2 (7.5 mg kg^{-1}, n = 14); 550.9 ± 46.2 (15 mg kg^{-1}, n = 14); and 512.9 ± 36.1 (30 mg kg^{-1}, n = 14). Statistical assessments show that the basal 5-HIAA levels did not differ significantly among the groups of animals. As can be seen from Figure 4, administration of vehicle produced no statistically significant changes in extracellular 5-HIAA concentration. Systemic administrations of sertraline (7.5, 15 and 30 mg kg^{-1}) produced statistically significant decreases in 5-HIAA contents in a dose-dependent fashion.

Discussion

The present study shows that sertraline decreased the intensity of the audiogenic seizures in a dose-dependent fashion in GEPR-9s. The data presented here also demonstrate that systemic administration of sertraline, at the same dose-range, increased dose-dependently the extracellular 5-HT concentrations in the thalamus of freely moving GEPR-9s. These findings confirm our earlier observation that drugs which increase functional extracellular 5-HT decrease convulsion intensity in GEPRs (Laird & Jobe, 1987; Dailey *et al.*, 1992b; Yan *et al.*, 1994b).

Upon comparing the time courses of anticonvulsant effect with those of extracellular 5-HT concentration, we found that a negative correlation existed between extracellular 5-HT concentration and audiogenic seizure intensity. Analysis showed that the slopes of the regression line for 15 and 30 mg kg^{-1} of sertraline are not statistically different from each other. This suggests that estimates of the change in 5-HT output in dialysates that produce a unit reduction in ARS are approximately the same, regardless of the dose of sertraline. The linkage between the sertraline-induced anticonvulsant effects and the increases in extracellular 5-HT suggests that enhancement of 5-hydroxytryptaminergic transmission may contribute to the anticonvulsant effects of sertraline in GEPR-9s.

Our previous studies have demonstrated that GEPRs have extensive deficiencies in central nervous system 5-hydroxytryptaminergic function (Dailey *et al.*, 1992a). In addition, we have found that several drugs with efficiency against sound-induced seizures in GEPRs produce an increase in extracellular 5-HT. Carbamazepine, antiepilepsirine (an anticonvulsant used clinically in China), loreclezole and fluoxetine produce anticonvulsant effects in GEPRs which appear to be mediated at least in part via an increase in extracellular 5-HT (Dailey *et al.*, 1992b; 1994; Yan *et al.*, 1992; Yan *et al.*, 1994a,b). Each of these drugs increases 5-HT levels in extracellular fluids. Depletion of 5-HT by inhibition of its synthesis greatly decreases the anticonvulsant effectiveness of carbamazepine, fluoxetine and antiepilepsirine (Yan *et al.*, 1992; 1994a). Other authors have shown that the broad-spectrum anticonvulsant, valproate, causes dose-related increases in extracellular 5-HT (Whitton & Fowler, 1991; Biggs *et al.*, 1992). Thus, some but not all established anticonvulsants increase extracellular 5-HT. Taken together, the data presented in this investigation are consistent with the view that sertraline is anticonvulsant in GEPRs because it blocks neuronal reuptake and increases functional extracellular 5-HT. These results are taken as further evidence to support the hypothesis that 5-HT plays an anticonvulsant role in GEPRs.

It is interesting to note that at 8 h after systemic administration of 30 mg kg^{-1} sertraline, the ARS still remained very low (ARS = 2.83) and extracellular 5-HT levels remained as high as 275% of pre-injection baseline. These findings are in agreement with the observations of Rutter & Auerbach (1993). They have shown that intraperitoneal injection of 10 mg kg^{-1} sertraline produced a significant increase in 5-HT in the diencephalon of freely moving Sprague-Dawley rats which lasted at least 24 h post-injection with approximately 250% of baseline at the eighth hour after the administration of the drug. Heym & Koe (1988) have indicated that intraperitoneal injection of a single dose of sertraline (10 mg kg^{-1}) results in greater than 50% inhibition of 5-HT uptake in brain for at least 8 h. The longer-lasting effects of sertraline may be due to the following facts: (1) The elimination half-life of sertraline is about 25 to 26 h (Murdoch & McTavish, 1992). (2) Demethyl-sertraline which is a major metabolite of sertraline is also a selective 5-HT uptake blocker and has an elimination half-life approximately 2.5 times greater than that of sertraline (Murdoch & McTavish, 1992). Its long elimination half-life makes sertraline suitable for once daily administration in clinical use.

Consistent with the previous studies (Manfridi *et al.*, 1992; Rutter & Auerbach, 1993), the present work shows that systemic administration of sertraline reduced dose-dependently extracellular 5-HIAA in the thalamus of freely moving GEPR-9s. This was to be expected considering that the majority of extracellular 5-HIAA results from intraneuronal 5-HT metabolism and that released 5-HT must be taken up into the neurone in order to be converted to 5-HIAA (Reinhard & Wurtman, 1977).

In conclusion, our recent work shows that sertraline is an effective anticonvulsant agent in GEPR-9s. Significant

increases in the extracellular 5-HT concentration occur after systemic administration of this drug. Temporal linkage exists between the magnitude of the anticonvulsant effects and the changes in the extracellular 5-HT concentration. These results support the concept that the anticonvulsant action of sertraline in GEPRs depends on enhancement of 5-hydroxytryptaminergic transmission. This study coupled with earlier investigations strongly suggests a role for 5-HT in the anticonvulsant effect in GEPRs.

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