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# Enhancement of the anticonvulsant effect of fluoxetine following blockade of 5-$HT_{1A}$ receptors

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**Abstract**

Serotonin reuptake inhibitors, such as fluoxetine, have been shown to exert anticonvulsant effects in several animal models of epilepsy. In view of recent studies showing that 5-$HT_{1A}$ receptor antagonists (somatodendritic autoreceptor antagonists) enhance the increase in extracellular 5-hydroxytryptamine (5-HT, serotonin) produced by serotonin reuptake inhibitors, it was of interest to determine if these antagonists also enhance the anticonvulsant effect of fluoxetine in Genetically Epilepsy-Prone Rats (GEPRs). The 5-$HT_{1A}$ receptor antagonists (−)-pindolol and LY 206130 (1-[1-H-indol-4-yloxy]-3-[cyclohexylamino]-2-propanol maleate) were examined in the present study and both enhanced the anticonvulsant action of fluoxetine in severe seizure GEPRs (GEPR-9s). The latter effect of LY 206130 was found to be dose- and 5-HT-dependent. These findings provide further evidence that the increase in extracellular serotonin observed after administering fluoxetine in combination with a 5-$HT_{1A}$ receptor antagonist is physiologically important and that the anticonvulsant effect of fluoxetine in the GEPR is mediated through an increase in extracellular 5-HT. © 1997 Elsevier Science B.V.

*Keywords:* Seizure; Fluoxetine; 5-$HT_{1A}$ receptor antagonist; 5-HT (5-hydroxytryptamine, serotonin); Epilepsy

## 1. Introduction

Treatments that enhance serotonergic neurotransmission in brain have been shown to exert anticonvulsant effects in a wide variety of experimental models of generalized epilepsy including the genetically epilepsy-prone rat (GEPR)(De La Torre et al., 1970; Jobe et al., 1973a; Buterbaugh, 1978). Conversely, treatments that reduce brain serotonin content have a proconvulsant effect in most of the same models (De La Torre et al., 1970; Jobe et al., 1973a; Kilian and Frey, 1973; Statnick et al., 1996). Among the treatments designed to increase the concentration of serotonin in the synaptic cleft, inhibition of serotonin reuptake with fluoxetine is highly effective (Fuller, 1994). Fluoxetine has also been shown to exert significant anticonvulsant effects on generalized tonic seizures (Buterbaugh, 1978; Dailey et al., 1992) as well as on secondarily generalized seizures (Prendiville and Gale, 1993). Moreover, the anticonvulsant effect of fluoxetine has been shown to be dependent on brain serotonin (Yan et al., 1994; Pasini et al., 1996).

Recent research has shown that the increase in extracellular serotonin (5-hydroxytryptamine, 5-HT) produced by systemic administration of fluoxetine or other selective serotonin reuptake inhibitors is attenuated when compared with the level of the increase observed after the local administration of fluoxetine into the region of the nerve terminals (e.g., hippocampus) (Hjorth, 1993; Rutter and Auerbach, 1993). Moreover, the focal administration of a 5-$HT_{1A}$ antagonist into the region of the serotonergic cell bodies (e.g., dorsal raphe nucleus) has been found to enhance the ability of systemically administered fluoxetine to increase extracellular 5-HT in the nerve terminal regions (Rutter and Auerbach, 1993). Thus, the lower effect of systemically administered serotonin reuptake inhibitors on nerve terminal accumulation of 5-HT is believed to result from the simultaneous accumulation of extracellular serotonin at the somatodendritic autoreceptors (5-$HT_{1A}$ subtype) in the raphe nuclei leading to a decrease in the firing

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rate of serotonergic neurons with a consequent reduction in 5-HT release in the terminal fields (Artigas et al., 1996). This autoreceptor mediated negative feedback can apparently be overridden by the blockade of somatodendritic (5-$HT_{1A}$) autoreceptors. Recently, Dreshfield et al. (1996) have shown that (−)-pindolol, a 5-$HT_{1A}$ and $\beta$-adrenoceptor antagonist, dose-dependently potentiates the fluoxetine dependent increase in extracellular 5-HT in the hypothalamus. Evidence that the increase in hypothalamic 5-HT is functionally important was provided by Fuller et al. (1996) who showed that the pindolol derivative and more selective 5-$HT_{1A}$ receptor antagonist LY 206130 (1-[1-H-indol-4-yloxy]-3-[cyclohexylamino]-2-propanol maleate) enhances the ability of fluoxetine to increase serum corticosterone in rats.

Existing evidence supports the concept that the anticonvulsant effect of fluoxetine in the Genetically Epilepsy-Prone Rat (GEPR) is mediated through an increase in extracellular 5-HT (Dailey et al., 1992). Accordingly, the concomitant administration of a 5-$HT_{1A}$ receptor antagonist should potentiate this effect. The present study was designed to determine if the blockade of somatodendritic 5-HT autoreceptors potentiates the anticonvulsant action of fluoxetine in the GEPR. To test this hypothesis we employed pindolol or LY 206130 in combination with a sub-anticonvulsant dose of fluoxetine in severe seizure genetically epilepsy-prone rats (GEPR-9s).

## 2. Materials and methods

### 2.1. Animals

The present studies were carried out in 250–350 g female severe seizure genetically epilepsy-prone rats (GEPR-9s) obtained from the breeding stock maintained at the University of Illinois College of Medicine at Peoria. They were housed two per cage on a 12 h light/dark cycle with food and water ad libitum. Each animal was used for more than one treatment. However, they were randomly assigned to treatment groups and there was a minimum of a 7 day interval between treatments in order to ensure that the drugs were eliminated prior to reuse. Any effect of repeated seizures on subsequent drug response was controlled in the experimental design, since control rats had the same number of seizures as the experimental group.

### 2.2. Drugs

Fluoxetine HCl, (−)-LY 206130 and (±)-LY 206130 were obtained from Eli Lilly (Indianapolis, IN, USA) and dissolved in double distilled water. Pindolol and parachlorophenylalanine were obtained from Sigma (St. Louis, MO, USA) and dissolved in 0.9% sodium chloride solution. All chemicals used in the monoamine assay were of HPLC grade and were obtained from Sigma.

### 2.3. Seizure testing

Rats were placed in a circular chamber constructed from galvanized metal and Plexiglas (40 cm in diameter by 50 cm in height). The sound was generated by two doorbells mounted on the inside of the lid. This system has been found to produce an intensity of about 100 db within the chamber. The sound stimulus was delivered for 60 s or until the convulsion began. The latency from the onset of the sound to the onset of the run and the convulsion were timed with a stopwatch. The seizure severity was scored using the system of Jobe et al. (1973b) as follows: 0 = no response; 1 = running only; 2 = clonus following two episodes of running; 3 = clonus following one episode of running; 4 = forelimb extension following two episodes of running; 5 = forelimb extension following one episode of running; 6 = forelimb extension and partial hindlimb extension following two episodes of running; 7 = forelimb extension and partial hindlimb extension following one episode of running; 8 = both forelimb and hindlimb extension following two episodes of running; 9 = both forelimb extension and hindlimb extension following one episode of running.

### 2.4. Serotonin depletion

In the present study, serotonin was depleted by the administration of parachlorophenylalanine (100 mg/kg, i.p.) per day for 3 days. Parachlorophenylanalnine injections were spaced 24 h apart and seizure testing with fluoxetine and LY 206130 was conducted 72 h after the last dose of parachlorophenylanalnine. Rats were then sacrificed for monoamine assay 4 h after the seizure test.

### 2.5. Analysis of brain monoamine concentration

Rats were sacrificed by decapitation and brains were removed, dissected into regions of interest and stored in liquid $N_2$ until assay. Brain regions were homogenized in 5 ml of 0.3 M perchloric acid and centrifuged at $13\,000 \times g$. One ml of supernatant was taken for 5-HT analysis while the remaining 4 ml were frozen for subsequent norepinephrine assay. 50 μl of supernatant were injected into a Bioanalytical high performance liquid chromatography (HPLC) system equipped with an ultrasphere 5 μ $C_{18}$ column and an electrochemical detector for detection of 5-HT according to the method of Mefford (1981). Quantitation of 5-HT was carried out by comparing samples to known standards. *N*-methyl-5-HT was used as an internal standard in the assay. A 2 ml aliquot of the remaining supernatant was taken for norepinephrine analysis. In the latter procedure 3,4-dihydroxybenzylamine was added to each sample as the internal standard. Norepinephrine was then extracted using acid-washed aluminum oxide at pH 8.6 and following elution from the aluminum oxide with 0.2 M perchloric acid was quantified using the HPLC

system described above according to the method of Browning et al. (1991a).

### 2.6. Statistical analyses

Seizure severity scores were compared between treated and control rats using a Mann–Whitney non-parametric analysis. Latencies to run and the seizure were compared using an analysis of variance with a Fisher or Scheffe post-hoc test. Brain monoamines in parachlorophenylalanine treated and control rats were compared using a *t*-test.

## 3. Results

### 3.1. Effects of pindolol on audiogenic seizures in GEPR-9s pretreated with a sub-anticonvulsant dose of fluoxetine

Rats receiving fluoxetine (15 mg/kg) or pindolol (10 mg/kg) alone displayed a seizure severity identical to that of vehicle injected controls (Fig. 1). However, as can be seen in Fig. 1, GEPR-9s pretreated with fluoxetine (15 mg/kg, 2 h before seizure) and pindolol (10 mg/kg, 30 min before seizure test) displayed a marked reduction in seizure severity as evidenced by the significant reduction in seizure score. Further evidence that pindolol enhances the anticonvulsant effect of fluoxetine is seen in Fig. 2 where the latency to both the onset of the run and the convulsion are found to be significantly prolonged. Such findings confirm what others have observed in other physiological systems (Fuller et al., 1996); namely, that the 5-$HT_{1A}$ receptor antagonist pindolol enhances the ability of fluoxetine to increase extracellular 5-HT in brain.

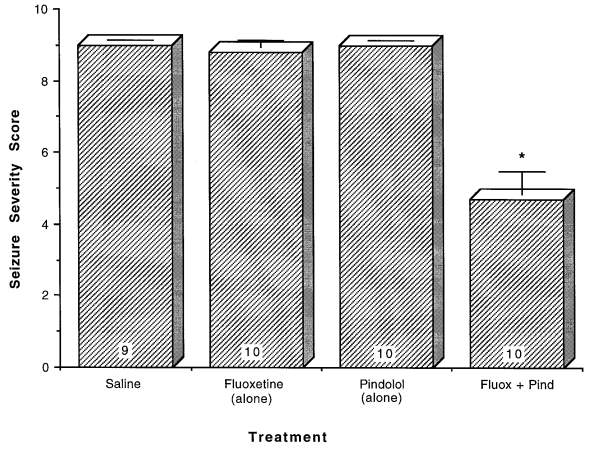


Fig. 1. Effect of fluoxetine (15 mg/kg) plus pindolol (10 mg/kg) on audiogenic seizure severity scores in GEPR-9s. Fluoxetine and pindolol were administered. i.p. 2 h and 30 min before seizure testing, respectively. Numbers inside bars indicate the number of rats in the group. Horizontal lines on top of bars indicate the standard error of the mean (S.E.M). The absence of error bars in the groups treated with saline and pindolol alone resulted from all animals in the group displaying a score of 9. * $P < 0.05$ compared to saline treated controls. Fluox = fluoxetine; Pind = pindolol.


Fig. 2. Effect of fluoxetine (15 mg/kg) and pindolol (10 mg/kg) on latency to run and latency to audiogenic seizure in GEPR-9s. Fluoxetine and pindolol were administered i.p. 2 h and 30 min before seizure testing, respectively. Numbers inside bars indicate the number of animals per group. Horizontal lines on top of bar indicate the S.E.M. * $P < 0.05$ compared to saline treated controls. Fluox = fluoxetine; Pind = pindolol.

### 3.2. Effect of LY 206130 on audiogenic seizures in GEPR-9s pretreated with a sub-anticonvulsant dose of fluoxetine

As can be seen in Fig. 3 the racemic form of the 5-$HT_{1A}$ receptor antagonist (±)-LY 206130 alone was ineffective in suppressing audiogenic seizures in GEPR-9s. However, when a sub-anticonvulsant dose of fluoxetine (15 mg/kg) was used in combination with the ineffective dose of (±)-LY 206130 (5 mg/kg) there was a marked reduction in seizure severity. Such findings confirm and extend those obtained with pindolol and provide additional support for the hypothesis that the anticonvulsant action of

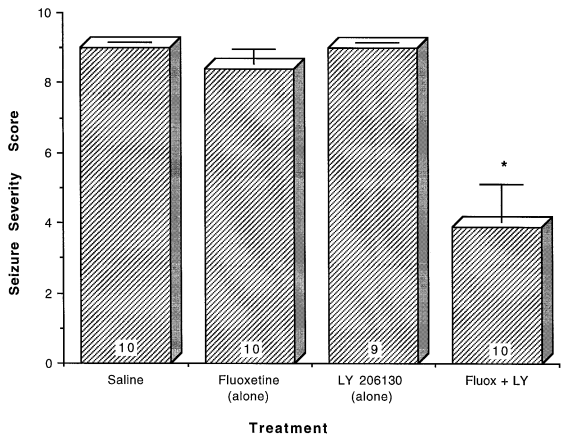


Fig. 3. Effect of fluoxetine (15 mg/kg) plus (±)-LY 206130 (5 mg/kg) on audiogenic seizure severity scores in GEPR-9s. Fluoxetine was administered i.p. 2 h before seizure testing, while (±)-LY 206130 was given subcutaneously 1 h before testing. Numbers inside bars indicate the number of rats per group. Horizontal lines on top of bar indicate the S.E.M. The absence of such lines in the groups treated with saline or (±)-LY 206130 alone resulted from all rats in the group displaying a score of 9. * $P < 0.05$ compared to saline treated control. Fluox = fluoxetine; LY = LY 206130.

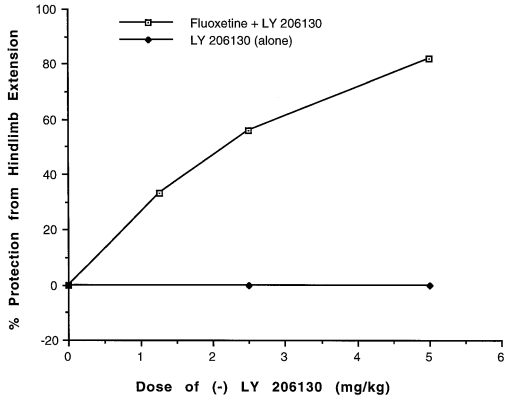


Fig. 4. Dose–response relationship between increasing doses of (−)-LY 206130 in the presence of fluoxetine (15 mg/kg) and the protection of GEPR-9s from tonic hindlimb extension. Fluoxetine was administered 2 h before and (−)-LY 206130 1 h before seizure testing. Routes of administration were the same as in Fig. 3. Control rats received saline + increasing doses of (−)-LY 206130.

fluoxetine is markedly enhanced in the presence of 5-$HT_{1A}$ receptor blockade. An analogous study was carried out using the minus (−) isomer of LY 206130 (i.e., the active form of the drug). As can be seen in Fig. 4, audiogenic seizure severity was reduced in a dose-dependent manner in animals pretreated with a sub-anticonvulsant dose of fluoxetine (15 mg/kg) and various doses of (−)-LY 206130.

### *3.3. Effect of parachlorophenylalanine on the anticonvulsant action of (−)-LY 206130 in GEPR-9s*

In order to determine if the anticonvulsant action of the (−)-LY 206130 and fluoxetine combination is mediated by an increase in synaptic serotonin, the anticonvulsant action of the two drugs was examined in rats pretreated

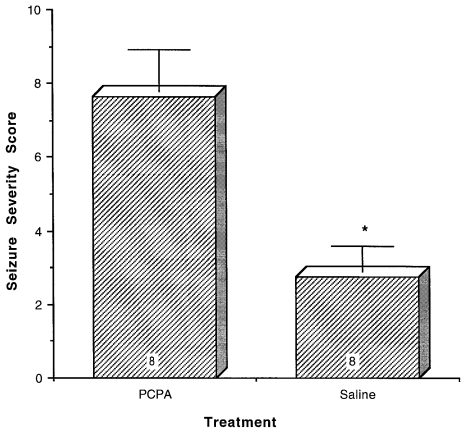


Fig. 5. Effect of parachlorophenylalanine (100 mg/kg×3) pretreatment on the anticonvulsant action of (−)-LY 206130 in GEPR-9s. Parachlorophenylalanine was administered intraperitoneally as described in Section 2. Numbers inside bars indicate the number of animals per group. Horizontal lines on top of bars indicate the S.E.M. An absence of error bars resulted when all rats in the group displayed a score of 9. * $P < 0.05$ compared to saline pretreated rats. PCPA = parachlorophenylalanine.

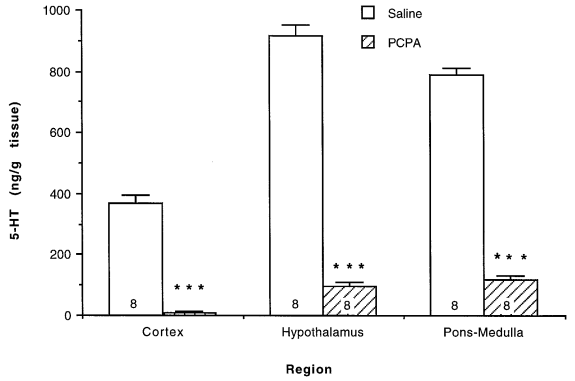


Fig. 6. Effect of parachlorophenylalanine treatment on regional brain 5-HT concentration. Numbers inside bars indicate the number of animals per group. Horizontal lines on top of bars indicate the S.E.M. Dose of parachlorophenylalanine was the same as in Fig. 5. *** $P < 0.001$ compared to saline treated rats. PCPA = parachlorophenylalanine.

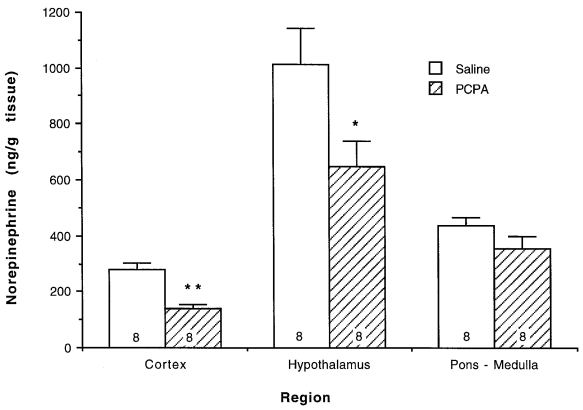


Fig. 7. Effect of parachlorophenylalanine treatment on regional brain norepinephrine. Numbers inside bars indicate the number of animals per group. These are the same animals whose brain 5-HT concentrations are shown in Fig. 6. Numbers inside bars indicate the number of rats per group. Horizontal lines on top of bars indicate S.E.M. * $P < 0.05$ compared to saline treated rats; ** $P < 0.001$ compared to saline treated control. PCPA = parachlorophenylalanine.

with parachlorophenylalanine to deplete brain 5-HT. As can be seen in Fig. 5, the combination of fluoxetine and (−)-LY 206130 was effective in rats pretreated with saline, but was ineffective in rats pretreated with parachlorophenylalanine (100 mg/kg per day for 3 days prior to fluoxetine treatment). This treatment with parachlorophenylalanine was found to be highly effective in depleting brain 5-HT. Serotonin concentration was lowered by 97% in cerebral cortex, 75% in hypothalamus and 69% in pons-medulla when measured 76 h after treatment with parachlorophenylalanine (Fig. 6). Norepinephrine was also reduced by 51% in the cortex and 36% in hypothalamus of GEPR-9s treated with parachlorophenylalanine, but was not significantly altered in the pons-medulla (Fig. 7).

## 4. Discussion

The present findings are consistent with the work of others showing that the increase in extracellular 5-HT

produced by selective serotonin reuptake inhibitors is greatly enhanced by the concomitant administration of a somatodendritic (5-$HT_{1A}$) autoreceptor antagonist (Hjorth, 1993). Moreover, they extend the findings of Fuller et al. (1996) showing that the increase in extracellular 5-HT produced by the combination of fluoxetine and LY 206130 is physiologically relevant. Indeed, in the former study the authors found that the increase in serum corticosterone was greater using the combination of fluoxetine and LY 206130 than with either drug alone. In the present study a sub-anticonvulsant dose of fluoxetine when administered with either pindolol or LY 206130 markedly reduced severity of sound-induced seizures in GEPR-9s. This was true using either the (−) isomer or the racemic form of LY 206130. The present findings are also in agreement with previous work showing that fluoxetine exerts impressive anticonvulsant effects on audiogenic seizures in GEPRs (Dailey et al., 1992), an effect that appears to be dependent on the accumulation of extracellular 5-HT (Yan et al., 1994).

Could the enhancement of fluoxetine's action by pindolol or LY 206130 in the present study be mediated by something other than the blockade of the somatodendritic 5-$HT_{1A}$ autoreceptor? Although this is possible, there are several reasons to believe that this is not the case. First, the effect was produced by two different drugs which share one action; namely, their ability to block 5-$HT_{1A}$ receptors. Secondly, neither pindolol nor LY 206130 had any effect on audiogenic seizures when used alone. Moreover, the well-known beta adrenergic blocking properties of pindolol could not have contributed to the effect, since activation rather than blockade of $\beta$-adrenoceptors antagonizes audiogenic seizures in GEPRs (Ko et al., 1984). Thirdly, the enhancement of fluoxetine's action by LY 206130 appears to have been mediated by 5-HT since it was not observed in rats depleted of 5-HT by pretreatment with parachlorophenylalanine.

One caveat associated with the present study was the use of the same animals in several experiments resulting in repeated exposure to fluoxetine and seizures. This was necessitated by limitations in the availability of GEPRs. The influence of prior exposure to drug and seizure was controlled in the experimental design by the use of 4 treatment groups each time, the random assignment of rats to a given group and an interval of at least 7 days between treatments. The relatively long half-life of norfluoxetine (the active metabolite of fluoxetine) in the body was of concern. However, inasmuch as the half-life of fluoxetine and norfluoxetine were found to be 5 and 15 h (Caccia et al., 1990), respectively, following an i.v. dose of 10 mg/kg of fluoxetine, more than 99% of both would have been eliminated in the 7 days between treatments. Additional evidence that repeated use of the animals did not influence the results was obtained by showing that rats receiving fluoxetine alone failed to differ from those receiving vehicle across tests. Finally, the findings have been replicated at least 3 times by virtue of the fact that the present study contained several experiments: (1) using the racemate of LY 206130, (2) using the minus isomer and (3) doing a dose–response study. Moreover, we have recently used the 5 mg/kg dose of (−)-LY 206130 in combination with fluoxetine (15 mg/kg) in a group of drug naive rats and obtained identical results (not shown).

The present study extends previous findings and provides further evidence that treatments designed to increase extracellular 5-HT exert anticonvulsant effects in GEPRs. Moreover, it provides additional evidence that the anticonvulsant effect of fluoxetine is mediated through 5-HT and not through some unknown action of this drug. Indeed, two pieces of evidence from this study appear to support this contention. First, two different drugs sharing one common action (blocking 5-$HT_{1A}$ receptors) both potentiated the anticonvulsant effect of fluoxetine. Second, the anticonvulsant effect of fluoxetine in combination with LY 206130 was abolished after depletion of brain 5-HT with parachlorophenylalanine. Although it is possible that the antagonism of the anticonvulsant effect of fluoxetine plus LY 206130 by parachlorophenylalanine was mediated, in part, through the depletion of norepinephrine rather than 5-HT, this seems unlikely. The depletion of norepinephrine by parachlorophenylalanine was restricted to forebrain regions, while 5-HT depletion occurred throughout the brain. Studies in our laboratory have previously found that while norepinephrine depletion throughout the brain has proconvulsant effects, selective depletion of the forebrain by as much as 70% failed to alter audiogenic seizures in GEPR-3s (Wang et al., 1994). This is consistent with other studies showing that the audiogenic seizure is a essentially a brainstem seizure that can occur independently of the forebrain (Browning et al., 1991b).

In summary, a sub-anticonvulsant dose of fluoxetine produced marked seizure suppression in GEPR-9s when administered in combination with a 5-$HT_{1A}$ receptor antagonist. The anticonvulsant potentiation produced by the 5-$HT_{1A}$ antagonist (−)-LY 206130 was found to be dose-dependent. The anticonvulsant effect produced by the combination of fluoxetine and (−)-LY 206130 appears to be mediated through an increase in extracellular 5-HT, since it was abolished by depletion of brain 5-HT. The present findings provide additional support for the hypothesis that the increased extracellular 5-HT resulting from the combination of fluoxetine and a 5-$HT_{1A}$ receptor antagonist is functionally important. In addition, the present study provides further support for the hypothesis that the anticonvulsant effect of fluoxetine in the GEPR is mediated through 5-HT.

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