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# Prolonged but not acute fluoxetine administration produces its inhibitory effect on hippocampal seizures in rats

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**Abstract** This study assessed the effects of acute as well as long-term administration of fluoxetine, a selective serotonin (5-HT) reuptake inhibitor with antidepressant properties, on hippocampal (HIP) seizures elicited by electrical stimulation in rats. The fluoxetine effect on HIP seizures was also assessed following long-term treatment with gepirone, a 5-$HT_{1A}$ receptor agonist. Acute single administration of fluoxetine (1, 10 mg/kg; IP) was found to produce no significant effect on HIP seizure activity. Following daily IP administration of fluoxetine (10 mg/kg per day) or gepirone (10 mg/kg per day) for 21 days, animals were given a 7-day drug-free period and then challenged with an acute dose of 10 mg/kg fluoxetine. These treatment regimens resulted in a significantly increased afterdischarge threshold of HIP seizures in response to acute fluoxetine administration. The inhibitory effect of fluoxetine, however, was not present 4 weeks after long-term treatment with either fluoxetine or gepirone. The present results indicate that long-term treatment with these compounds enhances the antiepileptic effect of subsequent fluoxetine administration on the generation of HIP seizures. This effect is possibly related to the well-demonstrated evidence that fluoxetine and gepirone, on long-term treatment, facilitate net 5-HT neurotransmission through desensitization of presynaptic 5-HT autoreceptors.

**Key words** Epilepsy · Serotonin · Fluoxetine · Gepirone · Long-term treatment · Hippocampus

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## Introduction

It has been thought that the serotonin (5-hydroxytryptamine, 5-HT) system is involved in the pathogenesis of depression and in its treatment (Meltzer and Lowy 1987). Although earlier studies produced conflicting results on the role of 5-HT in animal models of epilepsy (Kalichman 1982), our recent studies have provided evidence that the 5-HT system also plays an important role in regulating seizure activity (Wada et al. 1991, 1992, 1993a). Flouxetine is a selective 5-HT reuptake inhibitor which has recently been used as an antidepressant in clinical practice (Rickels and Schweizer 1990), and previous studies have shown antiepileptic properties of this agent in several animal models of seizures such as audiogenic seizures (Sparks and Buckholtz 1985; Dailey et al. 1992; Yan et al. 1994) and kindling (Wada et al. 1993b). In addition, Leander (1992) has shown that fluoxetine enhances the inhibitory effects of phenytoin, carbamazepine and ameltolide against maximal electroshock-induced convulsions in mice. It is known that long-term treatment with 5-HT reuptake inhibitors is required to obtain clinical efficacy in depressed patients (Rickels and Schweizer 1990), and long-term administration of these compounds has been suggested to enhance 5-HT neurotransmission in both animals (Blier and de Montigny 1983; Blier et al. 1984; de Montigny et al. 1984; Chaput et al. 1986; Welner et al. 1989; Bel and Artigas 1993) and humans (Charney and Heninger 1986). It would be important, therefore, to test the antiepileptic effects of long-term treatment with 5-HT reuptake inhibitors. To our knowledge, however, only one study has examined the effects of long-term fluoxetine administration on audiogenic seizures in genetically epilepsy-prone rats (Dailey et al. 1992).

In the present study, therefore, we examined the effect of acute as well as long-term treatment with fluoxetine on focal seizure activity induced by electrical stimulation to the rat hippocampus (HIP). We also

examined the fluoxetine effect on HIP seizures in rats chronically pretreated with gepirone, a 5-$HT_{1A}$ receptor agonist, which has been shown to possess antidepressant and anxiolytic properties (Csanalosi et al. 1987; Cott et al. 1988). A variety of compounds have been tested to characterize the action of both anticonvulsant and convulsant drugs in HIP seizure models (Burdette and Dyer 1987; Dragunow et al. 1987). In addition, anatomical data have shown a high density of 5-HT binding sites in the HIP (Köhler 1984; Peroutka 1988), suggesting that this model would be suitable for the investigation of the action of fluoxetine.

## Materials and methods

### Animals and surgery

Male Wistar rats, weighing 280–300 g at surgery, were used. Under sodium pentobarbital anesthesia (50 mg/kg, IP), a tripolar electrode was stereotaxically implanted into the CA1 region of the dorsal HIP. Coordinates were adapted according to the atlas of Paxinos and Watson (1986): A, − 3.6; L, 2.0; V, 2.7 (in mm), from the bregma. All tripolar electrodes consisted of three twisted nichrome wires (0.18mm in diameter) insulated except for the tip. A skull screw served as a reference electrode. Throughout the experiment, animals were housed individually and had free access to food and water.

### Electrical stimulation

One week after surgery, the afterdischarge (AD) threshold was determined. Electrical stimulation to the HIP was performed with a 2-s train of biphasic constant current, 60-Hz, sine wave pulses. The stimulus intensity was initially set at 10 μA peak-to-peak, and was subsequently increased by 10-μA steps each day until an AD was evoked. AD threshold was defined as the minimum current intensity necessary to elicit post-stimulus epileptiform discharges with amplitude being at least three times the prestimulus EEG. If no AD was evident with 100 μA stimulation, the rat was discarded from the experiment. The following experiments were conducted after ADs being reliably provoked by stimulation at the AD threshold on 5 consecutive days.

### Experiment 1: acute fluoxetine administration

Twenty rats were divided into three groups, and each rat received a single IP injection of 1 mg/kg fluoxetine ($n = 6$), 10 mg/kg fluoxetine ($n = 7$) or saline ($n = 7$). Drug and saline were injected IP in a volume of 2 ml/kg. Fluoxetine was dissolved in warm sterile 0.9% saline and was freshly prepared prior to each injection. One hour after fluoxetine or saline injection, electrical stimulation to the HIP was commenced at an intensity 10-μA below the previously determined AD threshold. If an AD was not evoked, the stimulus intensity was increased by 10-μA steps at 3-min intervals until an AD was elicited. AD duration was also measured from the end of stimulation train to the end of epileptiform discharges on EEG.

### Experiment 2: long-term drug treatment

Sixteen rats were divided into three groups, and each rat received IP injection once daily for 21 consecutive days with 10 mg/kg fluoxetine ($n = 5$), 10 mg/kg gepirone ($n = 5$) or 2 ml/kg saline ($n = 6$). These drugs were injected between 1600 and 1700 hours. On the day of the experiment, 1 week after the last injection of long-term treatment, a single dose of fluoxetine (10 mg/kg) was administered IP to the saline-, fluoxetine- and gepirone-pretreated rats. One hour later, stimulation was applied to each rat, and the AD threshold was determined using the same procedures as mentioned above. In this experiment, the fluoxetine effect was also examined 4 weeks after the long-term drug pretreatment.

Fluoxetine HCL and gepirone HCL were kind gifts from Eli Lilly (Indianapolis, Ind. USA) and Bristol-Meyers (Wellingford, Conn. USA), respectively.

Upon completion of these experiments, the rats were deeply anesthetized with pentobarbital, their brains perfused, serially sectioned, and stained for histological examination. All electrode tips were localized in the intended structure (i.e., CA 1 region of the HIP).

### Statistics

In both experiments, percent changes in the AD threshold and AD duration were calculated by comparing drug responses with baseline responses elicited in the same animal 1 day before single fluoxetine administration. Data were evaluated by one-way analysis of variance (ANOVA), followed by Scheffe's multiple comparison, to determine whether the percent changes significantly differed among the groups. Statistical significance was defined as $P < 0.05$.

## Results

### Experiment 1

The effects of acute IP administration of fluoxetine (1 and 10 mg/kg) on HIP seizure activity are shown in Fig. 1. One-way ANOVA showed no significant differences in the percent change values from baseline in the AD threshold among the three groups [$F(2, 17) = 1.176$, $P = 0.3325$]. Acute fluoxetine administration was also found to produce no significant changes in the AD duration [ANOVA, $F(2, 17) = 1.403$, $P = 0.2729$].

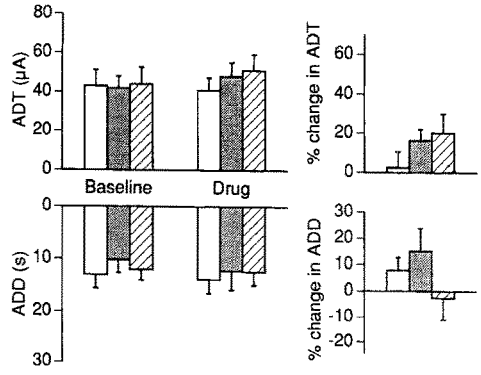


**Fig. 1** Effects of single IP administration of fluoxetine on electrically induced hippocampal seizures. Each value represents mean ± SEM obtained from rats treated with 2 ml/kg saline ($n = 7$), 1 mg/kg fluoxetine ($n = 6$) or 10 mg/kg fluoxetine ($n = 7$). Percentage changes were calculated by comparison of drug responses with baseline responses evoked in the same animal 1 day prior to drug administration. *ADT*, afterdischarge threshold; *ADD*, afterdischarge duration. □ saline 2 ml/kg, ▩ fluoxetine 1 mg/kg, ▨ fluoxetine 10 mg/kg

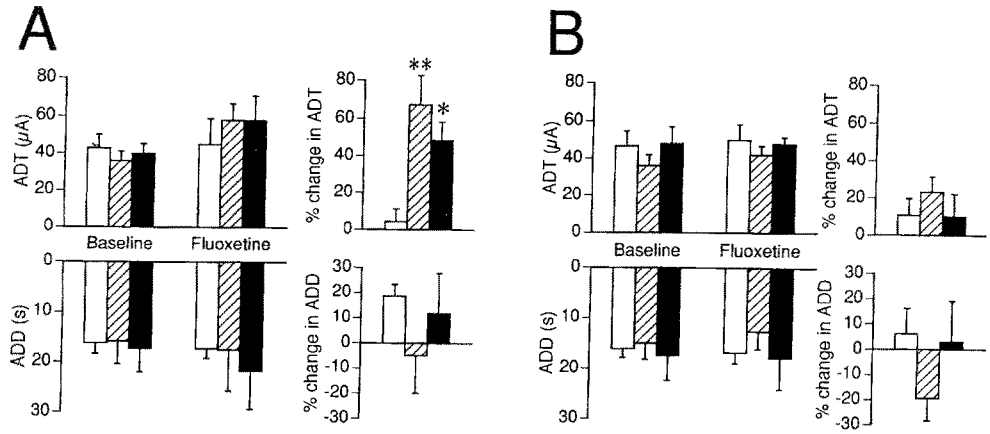


**Fig. 2A, B** Effects of long-term treatment with saline, fluoxetine or gepirone on seizure responses to a subsequent single administration of fluoxetine (10 mg/kg, IP). Seizure responses were tested 1 week (**A**) and 4 weeks (**B**) after long-term drug treatment. Each value represents mean ± SEM obtained from rats pretreated once daily for 21 days with saline (2 ml/kg, $n = 6$), fluoxetine (10 mg/kg, $n = 5$) or gepirone (10 mg/kg, $n = 5$). Percentage changes were calculated by comparison of drug responses with baseline responses evoked in the same animal 1 day prior to drug administration. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline-pretreated group (Scheffe's test). *ADT*, afterdischarge threshold; *ADD*, afterdischarge duration. □ saline 21 days, ▨ fluoxetine 21 days, ■ gepirone 21 days

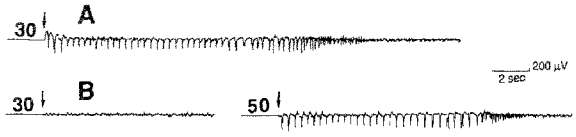


**Fig. 3A, B** EEGs showing the effect of 10mg/kg fluoxetine on hippocampal afterdischarge (AD) in a rat receiving a 21-day gepirone pretreatment. **A** AD evoked 1 day before fluoxetine injection; **B** AD evoked after fluoxetine injection. *Arrows* indicate cessation of the 2-s stimulation train. Numbers above stimulation indicate current intensity (in μA) applied to the hippocampus

Experiment 2

Figure 2 shows the effects of long-term pretreatment for 21 days with fluoxetine or gepirone on HIP seizure responses to a subsequent fluoxetine administration. One-way ANOVA showed a significant difference among the three groups in the percent change values in the AD threshold, measured 1 week after the last injection of long-term pretreatment [$F(2, 13) = 8.586$, $P = 0.0042$]. Single administration of 10mg/kg fluoxetine raised the AD threshold in all rats receiving long-term fluoxetine pretreatment, and post-hoc analysis by Scheffe's test showed that the fluoxetine-pretreated group had a significantly increased AD threshold when compared with the saline-pretreated group (67.3% versus 4.2%, $P < 0.01$, Fig. 2A). In the gepirone-pretreated group, a subsequent injection of fluoxetine also significantly increased the AD threshold when compared with the saline-pretreated group (48.3% versus 4.2%, $P < 0.05$, Fig. 2A). Figure 3 shows an example of changes in the AD threshold following single fluoxetine administration in a gepirone-pretreated rat. In contrast to the AD threshold, no significant difference was found in the percent change values in the duration of elicited ADs among the three groups [ANOVA, $F(2, 13) = 0.905$, $P = 0.4286$].

The inhibitory effect of fluoxetine was no longer present 4 weeks after the last injection of long-term drug pretreatment with either fluoxetine or gepirone. As shown in Fig. 2B, one-way ANOVA showed no significant percent changes among the three groups in either AD threshold [$F(2, 13) = 0.377$, $P = 0.693$] or AD duration [$F(2, 13) = 1.28$, $P = 0.311$].

## Discussion

The present study shows that the IP injection of fluoxetine (10 mg/kg), when tested 1 week after its repeated pretreatment for 21 days, produced a significant elevation in the AD threshold of electrically-induced HIP seizures (Fig. 2A). In contrast, the acute single injection of fluoxetine at doses of 1 and 10 mg/kg was found to produce no significant effect on the AD threshold (Fig. 1). These data suggest that long-term treatment with fluoxetine can enhance the antiepileptic effect of its subsequent administration on the generation of HIP seizures. The present findings are consistent with those of Dailey et al. (1992), who reported that the $ED_{50}$ value (determined by audiogenic seizure response score) after long-term fluoxetine administration for 28 days was lower than the acute $ED_{50}$ value in the rat model of sound-induced seizures. They stated, however, that the lower $ED_{50}$ after repeated fluoxetine administration apparently resulted from drug accumulation in the brain, because the fluoxetine effect was tested 4 h after administration of the 28th dose. In the present study, the inhibitory effect of fluoxetine was obtained 1 week after the last injection of its long-term

treatment. The plasma elimination half-lives of fluoxetine and its active metabolite (norfluoxetine) have been reported to be 5 and 15h in rats, respectively (Caccia et al. 1990). In addition, Gardier et al. (1994) demonstrated that fluoxetine and norfluoxetine were undetectable in the rat brain when measured 1 week after the cessation of a 21-day treatment with fluoxetine (10mg/kg per day). It is unlikely, therefore, that the accumulation of these compounds influenced the present results.

It is generally assumed that fluoxetine and other 5-HT reuptake inhibitors enhance 5-HT neurotransmission by inhibiting 5-HT reuptake into presynaptic nerve terminals (Rickels and Schweizer 1990). It is well known, however, that ascending 5-HT neurons are negatively controlled by 5-$HT_{1A}$ autoreceptors localized in the raphe nuclei (Sotelo et al. 1990) and terminal 5-$HT_{1B}$ autoreceptors (Middlemiss 1984; Engel et al. 1986), and electrophysiological studies have shown that 5-HT reuptake inhibitors, when administered acutely, can reduce the firing rate of 5-HT neurons and their terminal release possibly through the activation of presynaptic inhibitory autoreceptors (Rigdon and Wang 1987; de Montigny et al. 1990). It is therefore possible that the increased 5-HT availability is offset, or at least attenuated, by the decrease in the amount of 5-HT released, which may account for the lack of inhibitory action of acutely injected fluoxetine against HIP seizures.

On the other hand, there has been growing evidence that presynaptic 5-HT autoreceptors become desensitized following repeated treatment with 5-HT reuptake inhibitors. In contrast to the reduced firing rate of 5-HT neurons following acute administration, electrophysiological studies have shown that long-term treatment with 5-HT reuptake inhibitors results in a complete recovery of their firing activity (Blier and de Montigny 1983; Blier et al. 1984; de Montigny et al. 1984, 1990; Chaput et al. 1986). Based on their study using in vivo microdialysis, Bel and Artigas (1993) have recently suggested that chronic, but not acute, treatment with fluvoxamine, another 5-HT reuptake inhibitor, elicits a marked increase in synaptic 5-HT availability in projection areas. In addition, an autoradiographic study has shown that a 21-day treatment with fluoxetine at the same dose (10mg/kg per day) used in the present study reduces the density of 5-$HT_{1A}$ binding sites labeled with [$^3$H] 8-OH-DPAT in the raphe nuclei without altering HIP binding sites (Welner et al. 1989). There is also electrophysiological evidence suggesting the inhibitory properties of 5-HT on both spontaneous HIP neuronal activity (Segal 1975; Finch et al. 1978) and HIP seizures (Nishi et al. 1980; Cavalheiro et al. 1981). Taken together, these findings strongly suggest that long-term fluoxetine pretreatment can cause increased efficacy of 5-HT neurotransmission through the desensitization of presynaptic 5-HT autoreceptors, which results in the inhibition of HIP seizures.

The role of presynaptic autoreceptor desensitization in the seizure inhibiting mechanism of fluoxetine is further supported by the present finding that fluoxetine significantly increased the AD threshold in rats receiving long-term pretreatment with gepirone, a 5-$HT_{1A}$ receptor agonist (Fig. 2A). Long-term treatment with gepirone has also been demonstrated to induce the desensitization of presynaptic autoreceptors in the raphe nuclei, whereas postsynaptic 5-HT receptors in the HIP were found not to show any desensitization (Blier and de Montigny 1987, 1990). In addition, long-term gepirone treatment has been shown to reduce the density of 5-$HT_{1A}$ binding sites in the raphe nuclei but not in the HIP (Welner et al. 1989).

To our knowledge, no studies have dealt with the time course characteristics of the desensitization of 5-HT autoreceptors, although Blier and de Montigny (1987) reported that complete recovery of the firing rate of dorsal raphe 5-HT neurons was still present 2 days after cessation of a 14-day treatment with gepirone. In the present study, the inhibitory action of fluoxetine on HIP seizures was observed 1 week after long-term pretreatment with both fluoxetine and gepirone (Fig. 2A), suggesting that the desensitization of presynaptic 5-HT autoreceptors can persist for at least 1 week. However, the present study also showed that this inhibitory action was no longer obtained 4 weeks after long-term drug pretreatment (Fig. 2B). This may suggest that 5-HT autoreceptor desensitization is not a long-lasting effect, although further studies are needed to determine the precise mechanism.

In summary, the present study demonstrates that long-term pretreatment with fluoxetine or gepirone can potentiate the inhibitory effect of a subsequent administration of flouxetine on HIP seizure generation, suggesting that the desensitization of presynaptic 5-HT autoreceptors plays an important role in the seizure inhibiting mechanism of fluoxetine. Depression is a serious problem for epileptic patients, especially with temporal lobe epilepsy (Robertson 1985), and conventional antidepressant drugs are known to have epileptogenic potential (Trimble 1978; Edwards 1985). We therefore believe that fluoxetine and possibly other 5-HT reuptake inhibitors may produce significant therapeutic benefit in the treatment of depressive symptoms in patients with seizure disorders. It is well known that repeated administration of 5-HT reuptake inhibitors is required to obtain a clinically significant antidepressant effect (Rickels and Schweizer 1990). Given that the limbic system is implicated in the pathogenesis of mood disorders (Post and Uhde 1984), the present findings may relate to the delayed onset of the clinical efficacy of 5-HT reuptake inhibitors.

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