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Effect of acute administration of various 5-HT receptor agonists on focal hippocampal seizures in freely moving rats

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Abstract

In this study, we assessed the effects of the acute administration of various 5-HT receptor agonists on hippocampal partial seizures generated by low-frequency electrical stimulation in male Wistar rats. The seizure threshold and severity were determined by measuring the pulse number threshold and primary and secondary afterdischarges and the latency of secondary discharge was also determined. The administration (0.1–1 mg/kg, i.p.) of either the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-aminopropyl)tetralin (8-OH-DPAT), or the selective 5-HT_3 receptor agonist, 4-amino-(6-chloro-2-pyridyl)-1-piperidine (SR 57227A, 0.3–3 mg/kg, i.p.), did not alter any of the seizure parameters compared to those in vehicle-treated animals. Similarly, the administration of 0.3 and 1 mg/kg, i.p., of the 5-$HT_{2A,C}$ receptor agonist, (±)-2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI), did not alter any of the seizure parameters, whereas 3 mg/kg significantly decreased the latency of the secondary afterdischarge compared to that in vehicle-treated animals. The selective serotonin reuptake inhibitor, (±)-fluoxetine (2 mg/kg, i.p.), significantly increased the pulse number threshold and decreased the primary afterdischarge duration compared to those in vehicle-treated animals. In contrast, higher doses (6 or 20 mg/kg, i.p.) of fluoxetine did not significantly alter any of the seizure parameters measured. These results suggest that, in this model, stimulation of 5-HT_{1A}, 5-$HT_{2A,C}$ and 5-HT_3 receptors does not alter seizure threshold or severity and that the blockade of 5-HT uptake produced by a low dose of fluoxetine appears to increase seizure threshold and decrease seizure severity.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); Kindling; Hippocampus; Seizure

1. Introduction

In general, pharmacological treatments that enhance or attenuate serotonergic neurotransmission inhibit or augment epileptic seizures, respectively, in various animal models. For example, depletion of brain 5-hydroxytryptamine (5-HT) levels with *p*-chlorophenylalanine, an inhibitor of 5-HT synthesis, and the serotonergic neurotoxin, 5,7-dihydroxytrpytamine, exacerbates audiogenic-induced seizures in genetically epilepsy-prone rats (Jobe et al., 1973; Statnik et al., 1996). In addition, there is evidence that a deficit in serotonergic neurotransmission may play a role in the etiology of seizures in a subset of epileptic patients (Giroud et al., 1990; Pranzatelli et al., 1995; Shaywitz et al., 1975; Verma et al., 1984). In contrast, agents that enhance serotonergic neurotransmission, such as the selective serotonin reuptake inhibitors, fluoxetine and sertraline, have anticonvulsant action in aforementioned animals (Dailey et al., 1991; Laird and Jobe, 1987; Yan et al., 1994, 1995) and in females (Favale et al., 1995). It has been reported that seizures induced by kindling, maximal electroshock and pentylenetetrazol are attenuated by drugs that augment serotonergic tone (Buterbaugh, 1978; Lazarova et al., 1983, 1984; Wada et al., 1993). The systemic administration of certain anticonvulsants has been shown to increase extracellular levels of 5-HT as measured by in vivo microdialysis (Dailey et al., 1994; Whitton and Fowler, 1991; Yan et al., 1992) and fluoxetine enhances the anticonvulsant action of phenytoin and carbamazepine (Leander, 1992).

There is considerable evidence indicating that there are at least 14 subtypes of 5-HT receptors present in the mammalian central nervous system (for review, see the work of Hoyer et al., 1994). In addition, there are rela-

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tively selective receptor subtype agonists for some of the 5-HT receptors (Van Wijngaarden et al., 1990). Despite this, and the above evidence that 5-HT plays an important role in epileptic seizures, relatively few studies have examined the effect of specific 5-HT receptor agonists on seizures in animal models of epilepsy (Löscher and Czuczwar, 1985; Wada et al., 1992, 1993). Therefore, in this study, we examined the effect of the acute systemic administration of a 5-HT_{1A} receptor agonist, (±)-8-hydroxy-2-(di-*n*-aminopropyl)tetralin (8-OH-DPAT), the 5-$HT_{2A,C}$ receptor agonist, (±)-2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) and the 5-HT_3 receptor agonist, 4-amino-(6-chloro-2-pyridyl)-1-piperidine (SR 57227A), on hippocampally generated, partial seizures elicited by low frequency stimulation in freely moving male Wistar rats. The seizure threshold and severity of the seizures were determined by measuring pulse number threshold and the afterdischarge duration (primary and secondary). We also examined the effect of the selective serotonin reuptake inhibitor, (±)-fluoxetine. We used the low frequency, partially kindled hippocampal model for several reasons: (1) this procedure is advantageous as one can quantitatively measure epileptic afterdischarge threshold through a single stimulation train and obtain a stable afterdischarge threshold and duration (Emori and Minabe, 1990; Katsumori et al., 1996; Minabe and Emori, 1992; Minabe et al., 1993); (2) this model is believed to be an animal model of partial complex seizures as the behaviors observed after partial hippocampal kindling (Stage 1) in rats (Katsumori et al., 1996, 1998; Racine, 1972) is similar to that described for humans (McNamara, 1996); (3) partial complex seizures in humans appear to originate in the temporal lobe (which includes the hippocampus), an area enriched in 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 receptors (Pazos et al., 1985; Peroutka, 1988; Zifa and Fillion, 1992), as well as 5-HT nerve terminals; and (4) the administration of carbamazepine, one of the principal drugs used to treat partial complex seizures, increases the seizure threshold in this model, an effect indicative of anticonvulsant action (Katsumori et al., 1998).

2. Materials and methods

2.1. Animals

Male Wistar rats (Clea, Tokyo, Japan; $n = 48$), weighing 280 g at the time of surgery were used in all experiments. The animals were housed in plastic cages with wood-chip bedding in the animal care facility under constant temperature (23–25°C) and humidity (50–60%) on a 12-h light/12-h dark cycle (lights on at 0800 h). The animals were permitted access to food and water ad libitum. The experiments were conducted between 0900 and 1100 h.

2.2. Implantation of electrodes

The animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic frame. Tripolar electrodes (three twisted, 0.2-mm diameter polyurethane-coated stainless steel lines) were implanted bilaterally, with the tips placed in the dentate gyrus of the dorsal hippocampus (posterior 3.5 mm from bregma, lateral 2.0 mm from the sagittal sinus and ventral 4.0 mm from the cortical surface, according to Paxinos and Watson, 1986). Stainless steel screws were placed in the skull and served as anchors and reference electrodes. The electrodes were attached to the skull by dental acrylic cement and connected with a socket.

2.3. Stimulation procedure

After a post-operative period of 1 week, the animals received electrical stimulation pulses of 2 Hz for 12.5 s (biphasic square-wave pulses, 1 ms in duration at 500–800 μA, base-to-peak), using an automated, computer-assisted stimulation system (Nihon Koden, Sen-7103) and constant current units to elicit seizures. The stimulation frequency of 2 Hz was used because frequencies of 3 Hz or greater did not always permit us to determine the definitive onset of the afterdischarge due to the presence of stimulation artifacts on the electroencephalogram (EEG) recordings. All rats were stimulated once daily for 10 consecutive days without drug treatment. After determining that the seizure parameters were stable, the pharmacological experiments were conducted.

It is known that dentate gyrus kindling requires a greater number of electrical stimulations to progress than does conventional amygdaloid kindling and the behavioral seizure stage displays instability (Grace et al., 1990). However, preliminary experiments with our stimulation parameters indicated that seizure parameters such as afterdischarge duration and pulse number threshold, are stable during the period showing stage-1 seizures (i.e., immobility, facial grooming, wet-dog shake behavior or locomotion without a clonic component, based on the classification of Racine (1972)). Therefore, in our studies, we only used animals that showed stage-1 partial seizures.

The afterdischarge duration, which is indicative of seizure severity, was determined by measuring the total time of epileptic discharges (with an amplitude that is at least equivalent to the height of the pre-stimulation background on the EEG), i.e., the primary and secondary afterdischarges, present on the EEG (see Fig. 1). The interval between the end of the primary afterdischarge and the beginning of the secondary afterdischarge, is the latency of the secondary afterdischarge. The pulse number threshold, defined as the number of stimulating pulses required to elicit an afterdischarge, i.e., seizure threshold, was also measured (see Fig. 2). The behavior of the

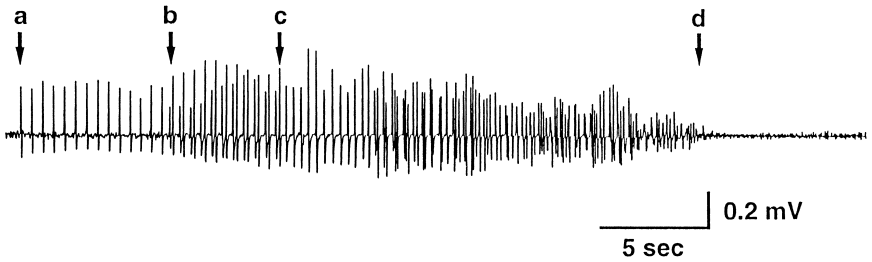

Fig. 1. Intracranial EEG recording from the dentate gyrus to the stimulation site during 2-Hz kindling stimulation; (a) Beginning of kindling stimulation; (b) Triggering of afterdischarge (AD); (c) Termination of stimulation; (d) The end of the primary AD. In this recording, the afterdischarge duration was the duration from (b) to (d).

animals was videotaped using an EEG-VTR system (Nihon Koden, VY-440A).

2.4. Evaluation of drug treatments

Animals received either vehicle (distilled water, 1 ml/kg) or 8-OH-DPAT (0.1, 0.3 or 1 mg/kg), DOI (0.3, 1 or 3 mg/kg), fluoxetine (2, 6 or 20 mg/kg) or SR 57227A (0.3, 1 or 3 mg/kg) i.p. 1 h before each stimulation. The doses of 8-OH-DPAT, DOI and SR 57227A used were based on the results of previous studies indicating that their maximal behavioral effects in rats were produced at doses between 0.5 and 1 mg/kg (Tricklebank et al., 1984), 1–2 mg/kg (Schreiber et al., 1994) and 1–3 mg/kg (Poncelet et al., 1995), respectively. The doses of fluoxetine chosen were based on previous ex vivo data indicating that the dose of fluoxetine required to decrease 5-HT uptake in the rat brain by 50% was 5–7 mg/kg, i.p. (Hyttel, 1994; Koe et al., 1983). The control recordings were done 2 days before (pre-drug controls) and 2 days after each drug treatment (post-drug controls). The effect of each treatment was evaluated by measuring pulse number threshold, primary and secondary afterdischarge duration and the latency of secondary afterdischarge. If an afterdischarge was not identified after low-frequency stimulation, 25 10-Hz stimulations were delivered to trigger an afterdischarge. In these cases, only the duration and latency were measured and the pulse number threshold was recorded as 25, i.e., the maximum number of stimulating pulses. If the same rat was to be used repeatedly in this experiment, we allowed at least 7 days to elapse between the injection of different drugs in order to avoid problems related to drug accumulation or drug–drug interactions.

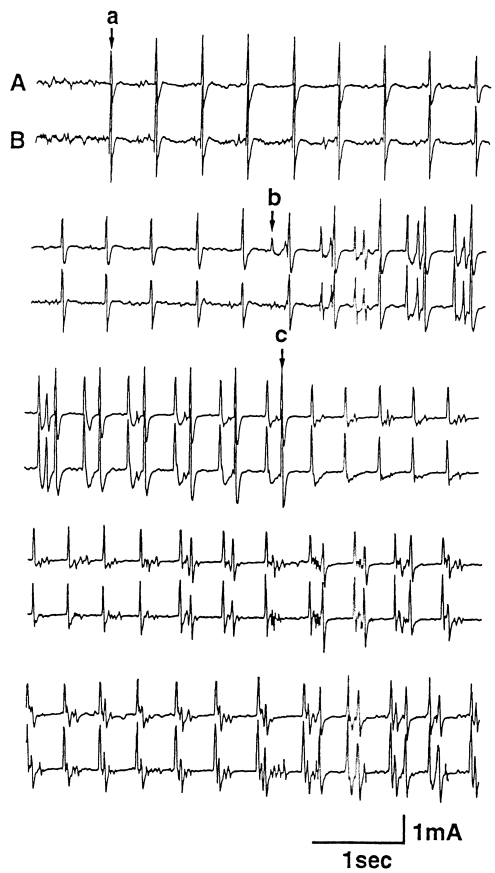

Fig. 2. Bilateral, intracranial EEG recording from the dentate gyrus during 2-Hz kindling stimulation. Consecutive tracings are shown from top to bottom. (A) Ipsilateral recording of stimulated side; (B) Contralateral recording; (a) Beginning of kindling stimulation; (b) Triggering of afterdischarge (AD); (c) Termination of stimulation. In this recording, the pulse number threshold (PNT) was 15 (the number of stimulating pulses from (a) to (b)).

2.5. Statistics

All the seizure parameter data were expressed as the mean ± S.E.M. The data from the pre-drug controls was compared to the post-drug controls using Wilcoxon's sign rank test for paired replicates.

2.6. Drugs

The compounds (±)-8-OH-DPAT HBr and (±)-DOI HCl were purchased from Research Biochemicals, (Natick, MA). SR 57227A HCl was purchased from Tocris-Cookson Chemicals (UK) and fluoxetine HCl was obtained from SmithKline and Beecham Pharmaceuticals.

3. Results

The injection of vehicle did not significantly alter any of the seizure parameters (data not shown). Furthermore,

Table 1
The effects of 5-HT receptor agonists and fluoxetine on seizure parameters of hippocampus-generating partial seizures in rats

Compound	Dose	*n*	Pulse number threshold			Primary afterdischarge duration (s)			Latency of secondary afterdischarge (s)			Secondary afterdischarge duration (s)		
			Pre-drug control	Drug	Post-drug control	Pre-drug	Drug	Post-drug control	Pre-drug	Drug	Post-drug control	Pre-drug control	Drug	Post-drug control
8-OH-DPAT	0.3 mg/kg	10	12.6±0.9	12.5±1.0	12.3±0.7	53.2±5.2	50.4±5.5	55.7±5.3	36.0±3.9	35.4±3.3	34.3±4.0	19.1±2.9	21.4±3.8	18.7±2.9
	1.0 mg/kg	7	12.3±0.9	12.06±0.9	12.7±0.8	53.3±6.1	52.3±5.2	56.3±5.2	39.9±5.3	43.6±4.8	35.6±5.2	15.9±3.2	14.9±4.2	20.3±5.0
DOI	0.3 mg/kg	8	11.8±0.7	12.4±0.8	11.6±0.8	43.8±5.6	49.0±7.1	49.8±6.5	43.8±5.2	37.8±6.1	42.9±5.4	17.8±5.0	16.1±4.0	16.8±4.9
	1.0 mg/kg	10	12.1±0.6	12.7±0.7	12.5±0.7	55.7±5.3	50.9±4.7	59.4±5.2	34.3±4.0	30.0±5.1	42.2±4.3	18.7±2.9	18.5±10.9	13.0±2.8
	3.0 mg/kg	9	11.6±0.8	11.3±0.9	10.0±1.4	49.6±3.0	52.6±3.4	50.6±3.7	37.1±4.3	15.9±2.8[b]	42.2±4.7	19.9±4.0	23.9±2.5	20.5±3.2
SR 57227A	0.3 mg/kg	9	11.5±0.6	11.2±0.7	11.9±0.8	57.7±3.8	52.5±3.8	60.6±5.3	38.0±4.7	36.7±4.6	38.8±4.6	16.5±2.8	18.2±3.1	18.1±3.2
	1.0 mg/kg	9	11.9±1.0	12.4±1.0	12.2±0.6	59.3±6.5	55.8±5.9	58.4±6.6	38.9±5.5	45.8±4.2	40.1±5.7	17.8±3.9	14.8±4.0	14.6±3.8
	3.0 mg/kg	10	11.9±0.3	12.0±0.9	11.7±0.3	62.4±7.9	58.3±5.2	68.7±9.0	48.7±3.8	37.9±3.6	37.3±3.9	12.7±3.2	14.5±3.0	17.4±3.5
Fluoxetine	2.0 mg/kg	9	12.1±0.9	13.1±0.8[a]	12.1±0.9	61.4±6.6	52.3±7.0[a]	57.7±4.7	36.0±4.3	38.9±4.8	36.8±3.9	13.2±3.0	11.7±2.7	12.9±2.8
	6 mg/kg	9	11.1±0.6	11.1±0.5	11.9±0.7	55.6±5.6	51.7±6.5	53.0±3.9	48.1±3.5	46.4±4.4	43.6±3.6	12.4±4.2	10.6±3.8	12.9±3.8
	20 mg/kg	10	11.8±0.6	11.9±0.7	12.0±0.8	52.2±3.9	65.5±9.2	56.8±6.1	40.4±4.1	35.3±5.9	35.9±3.4	15.9±3.9	14.2±3.9	15.8±3.4

Each value represents the mean±SEM.
[a,b]Significantly different from pre-drug control, $P < 0.05$ and 0.01, respectively; Wilcoxon signed-rank test.

there were no significant differences between the pre-drug and post-drug controls following the 48 h wash-out or withdrawal period.

3.1. The effects of 8-OH-DPAT

The intraperitoneal injection of 8-OH-DPAT produced a dose-dependent increase in forepaw treading, flat-body posture, straub tail and hyperlocomotion, i.e., the serotonin syndrome, as previously described (Hjorth et al., 1982; Tricklebank et al., 1984). After the 0.1 mg/kg dose, the rats were difficult to handle and to connect the electrode to the head-socket; therefore, we could not obtain enough data to analyze the results.

The intraperitoneal administration of either 0.3 or 1 mg/kg, i.p., of 8-OH-DPAT did not significantly alter pulse number threshold, primary or secondary afterdischarges or the latency of the secondary afterdischarge compared to the pre-drug controls (Table 1).

3.2. The effects of SR 57227A

Overall, the administration of SR 57227A did not produce any overt behavioral effects. The intraperitoneal administration of SR 57227A (0.3, 1 or 3 mg/kg) did not alter pulse number threshold, primary or secondary afterdischarges or the latency of the secondary afterdischarge compared to those in the pre-drug controls (Table 1).

3.3. The effects of DOI

As previously reported (Leysen et al., 1984; Schreiber et al., 1994), DOI produced a dose-dependent increase in headtwitching behavior (a rapid, rhythmic shaking of the head) and wet-dog shaking behavior. The intraperitoneal administration of 0.3 and 1 mg/kg of DOI did not alter pulse number threshold, primary or secondary afterdischarges or the latency of the secondary afterdischarge compared to those in vehicle-treated controls (Table 1). However, the 3 mg/kg dose of DOI significantly decreased (57%) the latency of the secondary afterdischarge compared to those in the pre-drug controls (Table 1).

3.4. The effects of fluoxetine

Fluoxetine did not produce any overt behavioral changes at the doses tested. Interestingly, at 2 mg/kg, but not at 6 or 20 mg/kg, fluoxetine produced a small, but significant increase in the pulse number threshold and a significant decrease (16%) in the primary after discharge duration (Table 1).

4. Discussion

4.1. 8-OH-DPAT

The results of our study indicated that the systemic administration of the 5-HT_{1A} receptor agonist, 8-OH-DPAT, did not alter the value of any of the seizure parameters in male Wistar rats with partial hippocampus seizures generated by low-frequency electrical stimulation. Thus, 8-OH-DPAT did not alter the threshold or the severity of seizures. To our knowledge, this is the first study examining the effect of 8-OH-DPAT on partial hippocampal seizures in freely moving rats. Similarly, 8-OH-DPAT produces a decrease in epileptiform activity induced hippocampal brain slices by bicuculline (Salgado and Alkadhi, 1995). However, it has been reported that the administration of 0.5 or 1 mg/kg, s.c., of 8-OH-DPAT to female Wistar rats does not alter the maximal electric shock threshold or amygdaloid-kindled seizures induced by electrical stimulation (Löscher and Czuczwar, 1985). Furthermore, 8-OH-DPAT (0.5 or 1 mg/kg, s.c.) does not alter seizure threshold in gerbils (Löscher and Czuczwar, 1985). Clearly, the result obtained in our study, unlike the ones indicating that 8-OH-DPAT elicits anticonvulsant-like actions (Gariboldi et al., 1996), indicate that 8-OH-DPAT does not display anticonvulsant activity in partially kindled, freely moving rats. The exact explanation for the discrepancy is unknown, but a reason could be differences in experimental design such as the model of epilepsy, the species used and the route of drug administration. It is possible that the differential stimulation of pre- and postsynaptic 5-HT_{1A} receptors is an important factor. For example, the stimulation of 5-HT_{1A} receptors in the hippocampus can suppress neuronal activity (Klancnik et al., 1991; Mason, 1985; Sprouse and Aghajanian, 1988), which could inhibit epileptiform activity generated by a number of experimental manipulations. However, the systemic and iontophoretic administration of 8-OH-DPAT elicits a decrease in the firing rate and activity of 5-HT neurons in the raphe nuclei (De Montigny et al., 1984; Sprouse and Aghajanian, 1987), an area with a high density of 5-HT_{1A} receptors (Pazos and Palacios, 1985; Jacobs and Azmitia, 1992) via activation of somatodendritic 5-HT_{1A} autoreceptors. This action could decrease the release of 5-HT from nerve terminals innervating areas such as the hippocampus and potentially promote seizure activity due to a decrease in 5-HT neurotransmission. Therefore, it is possible that, in our model, the administration of 8-OH-DPAT did not produce an anticonvulsant action because of the balance between its pre- and postsynaptic effects. Finally, it has been shown that 8-OH-DPAT has affinity for α_2-adrenoceptors ($pK_i = 6.5$) and dopamine D_2 receptors ($pK_i = 5.7$), although with lower affinity ($pK_i = 8.6$) than for 5-HT_{1A} receptors (Ruat et al., 1993; Van Wijngaarden et al., 1990) and this could potentially confuse the interpretation of the results.

4.2. DOI

Overall, the administration of 0.3 and 1 mg/kg, i.p., of DOI did not alter any of the seizure parameters determined after low frequency stimulation of the dentate gyrus. However, at the 3 mg/kg, i.p. dose, DOI significantly de-

creased the latency of the secondary afterdischarge compared to that in pre-drug controls, indicating that DOI lowers the seizure threshold. The role of the 5-HT_{2A} receptor in the generation of seizures remains to be elucidated. Using a model different from the one used in this study, Wada et al. (1993) reported that the administration of 1 mg/kg, i.p., of DOI significantly shortened the latency to generalized tonic–clonic seizures in female cats with hippocampal kindled seizures. The non-selective 5-HT_{2A} receptor antagonist, ketanserin, attenuates the anticonvulsant action of 5-hydroxytryptophan against seizures induced by electroshock in female Wistar rats, suggesting that 5-HT_{2A} may be involved in the decrease in seizure threshold (Löscher and Czuczwar, 1985). One might hypothesize that DOI would be expected to augment seizure activity, as activation of the 5-HT_{2A} receptor produces depolarization of neurons in the cortex and hippocampus. In addition, there is a high density of 5-HT_{2A} receptors in the cortex and hippocampus, both of which play a role in seizure generalization (Corcoran et al., 1975; Kudo and Wada, 1990) and DOI augments the excitatory postsynaptic potentials elicited by NMDA in rat cortical brain slices (Arvanov et al., 1996; Rahman and Neuman, 1993). One potential problem in interpreting data obtained with DOI is that it acts as a partial agonist at 5-HT_{2C}, in addition to stimulating 5-HT_{2A} receptors (Hoyer et al., 1989). Recent evidence has shown that mice lacking 5-HT_{2C} receptors express spontaneous seizures, have lower seizure threshold, rapid progression to seizures and are more sensitive to lethality produced by pentylenetetrazole administration (Applegate and Tecott, 1996; Tecott et al., 1995). However, we have shown that the acute administration of the 5-$HT_{2B,C}$ receptor antagonist SB 200646A does not significantly alter the pulse number threshold or afterdischarge duration of hippocampal partial seizures in male Wistar rats (Watanabe et al., 1997). Clearly, it would be of interest to examine the effects of selective 5-HT_{2C} and 5-HT_{2A} receptor agonists, which are currently not available, in our model.

4.3. SR 57227A

The systemic administration of the selective 5-HT_3 receptor agonist, SR 57227A (Bachy et al., 1993), did not alter any of the seizure parameters, indicating that in this model, 5-HT_3 receptors are not involved in modulating partial seizures in freely moving Wistar rats. This is the first study to examine the effect of a selective 5-HT_3 receptor agonist on partial hippocampal seizures. A recent report has shown that in contrast, the intracerebroventricular administration of the 5-HT_3 receptor agonist, 1-(*m*-chlorophenyl)-biguanide (*m*-CPBG), increased the duration of afterdischarge of generalized kindled seizures elicited by electrical stimulation of the amygdala in male Wistar rats (Wada et al., 1997). However, it may be difficult to compare the results as our animals only displayed stage 1 seizures and we administered our drug systemically as opposed to the intracerebroventricular route. It is unlikely that the lack of effect in our study was related to the doses given or to problems with penetration into the brain, as the data indicate that at doses of 1 or 3 mg/kg, i.p., SR 57227A produces an antidepressant action in rats (Poncelet et al., 1995) and penetrates the blood-brain barrier. Furthermore, it has been shown that the i.p. dose of SR 57227A required to occupy 50% of the receptors in the cortex is 0.4 mg/kg and about 65–70% of the 5-HT_3 receptors are occupied 1 h after administration (Bachy et al., 1993).

4.4. Fluoxetine

The results of our study indicated that the systemic administration of a low dose of fluoxetine (2 mg/kg, i.p.), a selective 5-HT reuptake inhibitor (Wong et al., 1974, 1995), produced a significant increase in the pulse number threshold and a decrease in the secondary afterdischarge. Thus, our data indicate that fluoxetine has an anticonvulsant action on partially kindled seizures generated in the hippocampus of male Wistar rats. Since fluoxetine would ultimately increase 5-HT levels in the synapse, it is postulated that its anticonvulsant action is related to stimulation of postsynaptic 5-HT receptors. Our results suggest that fluoxetine's action is unlikely to be related to stimulation of 5-HT_{1A}, 5-HT_3 or 5-$HT_{2A,C}$ receptors, although one cannot rule out the involvement of other 5-HT receptor subtypes. Further studies must be conducted to elucidate which 5-HT receptor(s) play a role in mediating fluoxetine's action.

Our findings with fluoxetine are consistent with those from other studies with various animal models of seizures (Dailey et al., 1991; Sparks and Buckholtz, 1985; Yan et al., 1994, 1995). However, in the present study, only the 2 mg/kg, but not either the 6 or 20 mg/kg doses, displayed an anticonvulsant action. In contrast, in genetically epilepsy-prone rats, the ED50 of fluoxetine after acute and chronic administration was 15.9 and 8.2 mg/kg, i.p., respectively (Dailey et al., 1991). Furthermore, sertraline, another selective serotonin reuptake inhibitor (Koe et al., 1983; Hyttel, 1994), produces a dose-dependent (7.5–30 mg/kg, i.p.) decrease in audiogenic seizures (Yan et al., 1995). Currently, the explanation as to why a low dose of fluoxetine, but not the higher doses, exhibited an anticonvulsant action in our model, is unknown. It is possible that the differences in doses required to produce an anticonvulsant action between our model and the genetically epilepsy-prone rats is related to differences in the etiology of the seizures. Indeed, there is evidence that genetically epilepsy-prone rats have a relative deficiency of 5-HT in certain brain areas, whereas this remains to be shown for partial seizures of the hippocampus. Another argument relates to the increase in 5-HT levels produced by each dose. For example, the acute administration of 2, 5, 10 and 40 mg/kg produces a 0.5–1, 1–1.5, 2–5 and 4-fold increase in extracellular 5-HT levels, respectively, in vari-

ous areas of the rat brain (Fuller, 1994; Perry and Fuller, 1992; Rutter and Auerbach, 1993). Thus, it is possible that at the 2 mg/kg dose, the increase in 5-HT may only lead to the stimulation of 5-HT receptor subtypes that are involved in suppressing seizures, whereas at the higher doses, 5-HT may be stimulating receptors that are involved in producing seizures as well as those that suppress seizures, i.e., a counterbalancing action. However, this remains to be experimentally verified.

5. Conclusion

Our results indicate that the systemic administration of the 5-HT_{1A} or of the 5-HT_3 receptor agonists, 8-OH-DPAT or SR 57227A, does not produce anticonvulsant actions in the animals with focal hippocampal seizures generated by low-frequency stimulation. In contrast, the 2 mg/kg, but not the 6 or 20 mg/kg doses of fluoxetine, produced a small, but significant increase and decrease in seizure threshold and severity, indicating that fluoxetine has anticonvulsant activity, although the exact mechanism remains to be elucidated. The systemic administration of 3 mg/kg, i.p., of DOI produced a decrease in the latency of the secondary afterdischarge, indicating that seizure threshold is decreased by stimulation of 5-$HT_{2A,C}$ receptors. Additional studies with other selective 5-HT receptor agonists (e.g., 5-HT_4, 5-HT_{1B}) should be conducted to gain further insight into the role of 5-HT in seizure activity.

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