Seizure 45 (2017) 119–124

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The effect of sertraline and 8-OH-DPAT on the PTZ_induced seizure threshold: Role of the nitrergic system

Azhdar Heydari, Shima Davoudi*

Physiology Research Center, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran

ARTICLE INFO

Article history:
Received 22 August 2016
Received in revised form 2 December 2016
Accepted 5 December 2016
Available online xxx

Keywords:
Sertraline
Seizure
$5HT_{1A}$ receptor
Nitric oxide
L-NAME
Pentylenetetrazole

ABSTRACT

Purpose: Serotonin is a key regulatory neurotransmitter in the CNS which plays an important role in seizure through different receptors, especially the $5HT_{1A}$ subtype. The role of sertraline through the $5HT_{1A}$ receptor and nitric oxide interaction on the PTZ-induced seizure threshold was investigated in this study.
Method: In this study, 70 white male mice were randomly divided into 10 groups including intact control, sham-control and eight experimental groups which received sertraline, 8-OH-DPAT, WAY100635, WAY100635 + sertraline, WAY100635 + 8-OH-DPAT, L-NAME, L-NAME + sertraline and L-NAME + 8-OH-DPAT. After 14 days of treatment in different groups, the PTZ-induced seizure threshold was assessed and the measurement of nitric oxide metabolites in the brain tissue was done with the Greiss method.
Results: The seizure threshold was significantly increased in the sertraline and 8OH-DPAT receiving groups compared to the sham group (P 0.001). In the presence of WAY100635, the effect of both sertraline and 8-OH-DPAT in raising the seizure threshold was more prominent (P 0.001) but on the other hand, in the presence of L-NAME, an increase in the anticonvulsant effect of 8-OH-DPAT was observed, while L-NAME alone had no effect on the seizure threshold (P 0.001). The NO_X concentration was significantly decreased in the 8-OH-DPAT_treated group (P 0.01), while the WAY100657 reversed it and the combination of 8-OH-DPAT with L-NAME reduced the NO_X levels (P 0.001).
Conclusions: These findings support the anticonvulsant effect of SSRIs and selective $5HT_{1A}$ receptors, although serotonin receptors other than $5HT_{1A}$ subtype may be involved and also it is probable that some anticonvulsant effects of the sertraline and 8-OH-DPAT are through the modulation of nitrergic system.

1. Introduction

Serotonin or 5-hydroxytryptamine is a monoamine neurotransmitter derived from hydroxylation and decarboxylation of L-tryptophan [1–3] and can regulate various physiological and behavioral processes [4,5]. Each type of disturbance in the synthesis, metabolism or reuptake of serotonin may lead to neurological disorders such as migraine, Alzheimer's disease, depression and seizure [6–8]. Serotonin has seven families of receptors ($5HT_1$ to $5HT_7$) that may be involved in different types of seizures [9,10]. Serotonergic projections which are extensive in the anterior brain and brain stem structures [9].

Among various subtypes of serotonin receptors ($5HT_1$ to $5HT_7$), the $5HT_{1A}$ receptor plays an important role in seizures [11]. In the mammalian brain, the $5HT_{1A}$ receptor has pre- and post-synaptic distribution [12]. Activation of the $5HT_{1A}$ autoreceptor diminishes the activity of serotonergic neurons and thereby decreases the release of serotonin. In contrast, the activity of the postsynaptic $5HT_{1A}$ receptors mimics the effects of the serotonin release and facilitates serotonin transmission [13,14]. Unfortunately in acute seizures with a natural hippocampus, the effect of the $5HT_{1A}$ receptor is still controversial [15]. In different seizure models, the $5HT_{1A}$ receptor can have exerts anticonvulsant [16,17] and proconvulsant effects [18] or even it can have a neutral effect [19,20] on seizure.

Nitric oxide (NO) is synthesized from L-arginine by the nitric oxide synthase (NOS) [21] and plays an important role in the normal action of the brain [22]. Although it has shown its anticonvulsant or proconvulsant properties in different seizure models but its role in seizure is not completely clear [23].

Recently, the interaction between the 5-HT receptor subtypes and NO has been proposed [21]. Some selective serotonin reuptake inhibitors (SSRIs) such as paroxetine act as an NOS inhibitor [24]. On the other hand, some NOS inhibitors such as L-N^G-Nitroarginine

* Corresponding author.
E-mail address: shimadavooooodi@gmail.com (S. Davoudi).

http://dx.doi.org/10.1016/j.seizure.2016.12.005
1059-1311/

methyl ester (L-NAME) have antidepressant effect and boost the effect of SSRIs. The $5HT_{1A}$ agonists such as 8-OH-DPAT downregulate nNOS expression and leads to a decrease in NO, an effect which is blocked by application of the 5- HT_{1A} receptor antagonists. These findings suggest that NO may be a downstream signaling molecule of 5-HT [25]. A model of the 5-HT_{1A} receptor-nNOS-CREB pathway has been proposed in some studies [24,25]. In the present study, we examined the effect of chronic administration of sertraline and 8-OH-DPAT on the PTZ-induced clonic seizures threshold in male mice. Regarding the functional interactions of 5HT with NO signaling pathway and the fact that both sertraline and 8-OH-DPAT are the $5HT_{1A}$ receptor agonist, we further investigated the possible involvement of NO in the modulatory effect of these compounds on the seizure susceptibility by using L-NAME.

2. Method

All experiments were performed in accordance with the guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985). They were also approved by the Research and Ethics Committee of Kashan University of Medical Sciences, Kashan, Iran. White male mice (25–30 g) were bred in the animal house of Physiology Research Center, Kashan University of Medical Sciences. They were housed in the standard polypropylene cages under standard temperature (25 degC) and humidity (%50–60) with a 12 h light and 12 h dark cycle. They were fed standard mouse food with ad libitum access to water. Animals were divided randomly into ten groups (n = 7 in each group) including intact control, sham-control and eight experimental groups which received sertraline, 8-OH-DPAT, WAY100635, WAY100635 + sertraline, WAY100635 + 8-OH-DPAT, L-NAME, L-NAME + sertraline and L-NAME + 8-OH-DPAT.

2.1. Chemicals and drugs

The drugs used were PTZ, sertraline, 8-OH-DPAT, WAY100635 and L-NAME. All the above_mentioned drugs except sertraline were purchased from Sigma (USA). Sertraline was purchased from Darupakhsh (Tehran/Iran).

2.2. Procedure

PTZ(0.5% solution) was prepared in 0.9% saline and administered as intravenous infusion. In addition, sertraline was prepared at carboxymethylcellulose(CMC, 0.5%) as a solvent agent and administered orally by gavage for 14 days.

Other drugs were dissolved in normal saline solution at desired concentration and administered intraperitoneally (IP), in a volume of 10 ml/kg of body weight.

The doses of sertraline, 8-OH-DPAT, WAY100635 and L-NAME were chosen based on the previous studies and pilot experiments. WAY100635 was injected 30 min before the administration of sertraline or 8-OH-DPAT.

2.3. Seizure induction

PTZ was dissolved in heparinized sterile saline (0.9%) to prepare a fresh solution with a concentration of 5 mg/ml before an intravenous (IV) infusion. The dose and infusion rate of the administered PTZ was 5 mg/ml and 0.5 ml/min, respectively [26]. Before testing, each mouse was weighed and placed in a clear acrylic plastic restrainer and then its tail was immersed in a warm water bath (40–45 degC) for 1 min to dilate the tail veins. A dental carpule (30 G) connected by a polyethylene tube (No. 10) to a 10 ml syringe prefilled with heparinized PTZ solution was used. The needle was inserted into the mid length of the lateral tail vein and during the infusion period, the animal could move freely with the aid of attached canula. Each animal was observed throughout the infusion period and the duration time between the start of infusion and onset of clonic seizures was recorded in seconds and converted to the threshold convulsant dosage by the following formula [27]:

$$\text{Seizure Threshold} = \frac{\text{Concentration (mg/ml)} \times \text{Infusion Rate (ml/min)} \times \text{Time (s)} \times 1000}{\text{Weight (g)} \times 60}$$

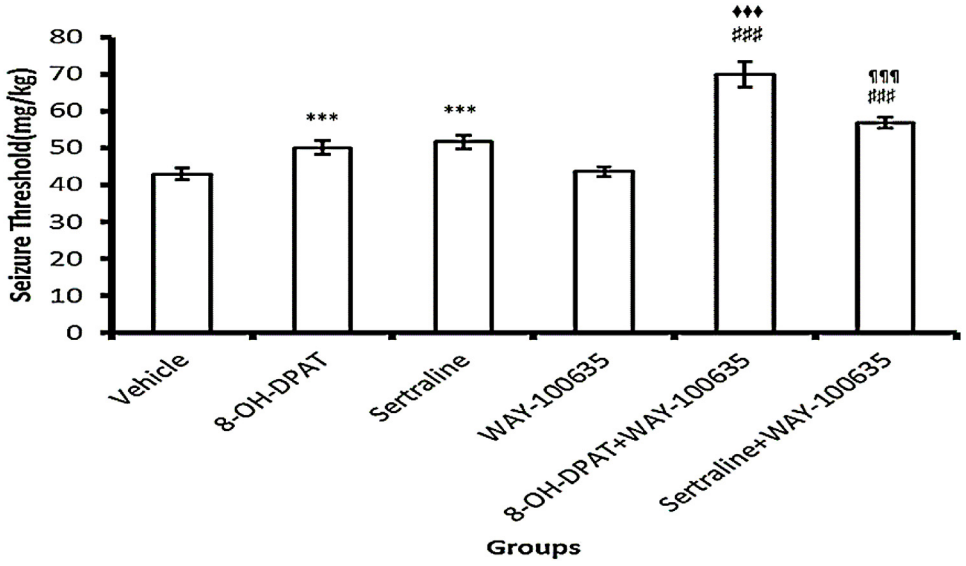

Fig. 1. The effect of chronic pre-treatment with WAY-100635 in combination with 8-OH-DPAT or sertraline treatment on the seizure threshold. The seizure threshold was significantly increased in treatment with 8-OH-DPAT or sertraline. This effect also was potentiated with pre-treatment by WAY100635 in combination with 8-OH-DPAT or sertraline. ***P 0.001 compared to vehicle. P 0.001 compared to 8-OH-DPAT group. ¶¶¶ $P < 0.001$ compared to sertraline group. ### $P < 0.001$ compared to WAY100635 group.

2.4. Measurement of total nitrate and nitrite (NOx)

The assay described by Miranda et al. [28] was used to reduce nitrate to nitrite by vanadium (III) chloride, followed by the spectrophotometric analysis of total nitrite using Greiss reagent. For the measurement of nitric oxide metabolites in the brain tissue samples, 1 gram of brain tissue was homogenized in 10 ml of Tris Hcl 50 M, containing 0.1 mM EDTA and the homogenized suspension was deproteinized by trichloroacetic acid (10%) to reduce turbidity. Experiments were performed at room temperature, as noted. A nitrate standard solution (100 ml) was serially diluted (from 20 to 100 M) in a 96-well microplate. First, plate loaded with samples (100 l) and VCl3 (100 l), then sulfanilamide (50 l) and NEDD (50 l) were added to each well and at last diluting medium was used to determine blank values. It should be noted that the absorbance at 540 nm was measured by using a plate reader following the incubation (45 min) [29].

2.5. Statistical analysis

All results were expressed as mean values SEM. Statistical analysis of the results was done by one-way ANOVA for the seizure thresholds followed by Tukey's test for multiple comparisons. Differences were considered significant if the P value were less than 0.05.

3. Results

Fig. 1 illustrates the effects of 14 days sertraline (10 mg/kg) or 8-OH-DPAT (1 mg/kg) administration on the PTZ-induced seizure threshold. The clonic seizure threshold was increased significantly in both sertraline and 8-OH-DPAT treated groups compared to the vehicle (P 0.001). WAY100635, the specific $5HT_{1A}$ receptor antagonist (0.3 mg/kg, i.p) alone did not alter the PTZ-induced clonic seizure threshold. Unexpectedly, the combination of WAY100635 (0.3 mg/kg, i.p) with 8-OH-DPAT or sertraline, potentiated the anticonvulsant effect of both drugs.

Fig. 2 illustrates the effects of 14 days L-NAME administration (50 mg/kg) alone and in combination with sertraline (30 mg/kg) or 8-OH-DPAT (1 mg/kg). Sub-effective dose of L-NAME (50 mg/kg) failed to show anticonvulsant activity. The co-administration of L-NAME (50 mg/kg) with 8-OH-DPAT (1 mg/kg) significantly increased the PTZ-induced seizure threshold, while the co-administration of L-NAME (50 mg/kg) with sertraline (10 mg/kg) had no effect on the seizure threshold.

Fig. 3 shows the brain tissues concentration of NOx in the L-NAME treated groups. L-NAME at sub-effective concentration (50 mg/kg) significantly decreased the NOx concentration compared to the sham control group (p 0.01).

The brain tissues concentrations of NOx in 8-OH-DPAT treated group was significantly lower than sham group and the co-administration of sub-effective of L-NAME(50 mg/kg) with 8OH-DPAT(1 mg/kg) further decreased NOx concentration. Sertraline (10 mg/kg) alone or in combination with sub-effective concentration of L-NAME (50 mg/kg) had no significant effect on NOx concentration.

4. Discussion

In the present study, we investigated the effect of sertraline (a SSRI inhibitor) and 8-OH-DPAT (a specific $5HT_{1A}$ receptor antagonist) on the PTZ-induced clonic seizure threshold. The results showed that both sertraline and 8OH-DPAT significantly increased the PTZ-induced clonic seizure threshold in mice.

Some studies indicate that serotonin has a protective effect against epilepsy in the central nervous system and some SSRIs have anticonvulsant effect [30]. Loscher showed that the stimulation of $5HT_{1A}$ receptor with SSRIs had protective effects against seizures [31]. Although some studies have shown that the anticonvulsant effect of SSRIs is not solely mediated through the $5HT_{1A}$ receptor [32,33].

SSRI family has been found to possess antiepileptic properties in human and animal models of epilepsy [34].

The primary effect of SSRIs is increasing 5HT in the synaptic cleft. The results of animal studies show that 5-HT plays an important role in the neural excitability, epileptogenesis, and seizure propagation [35,36]. Among the SSRIs, sertraline was selected, because it has the lowest reported seizure occurrence [37] and can be safely used in the vast majority of epileptic patients [38].

In accordance with the sertraline increased the PTZ-induced seizure threshold in this study, studies showing that agents such as SSRIs have antiepileptic effect through the increase of extracellular 5-HT [11,39], just like sertraline, 8OH-DPAT increased the PTZ-induced seizure threshold. The activation of $5HT_{1A}$ receptors inhibits adenylyl cyclase and decreases cAMP production. It also

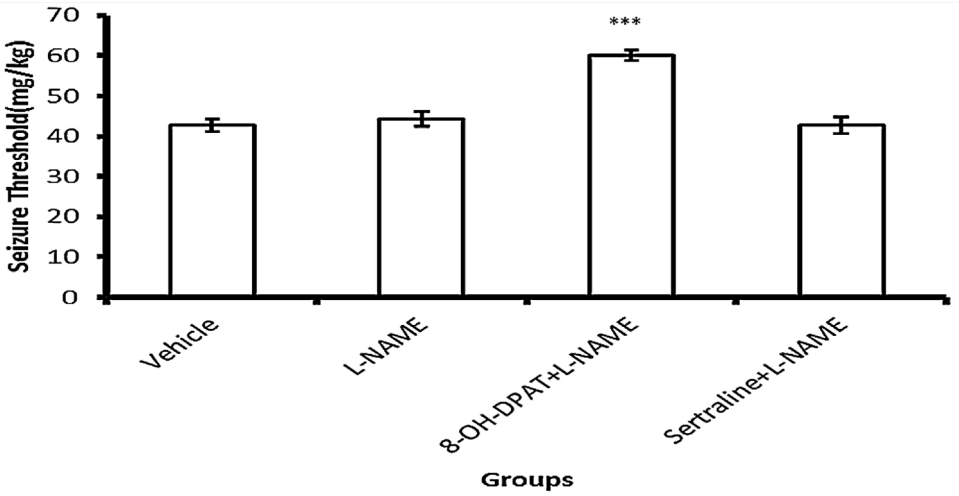

Fig. 2. The effect of chronic pre-treatment with L-NAME alone and in combination of 8-OH-DPAT or sertraline on the seizure threshold. The seizure threshold was significantly increased in pre-treatment with L-NAME in combination with 8-OH-DPAT but this effect was not observed with pre-treatment with L-NAME alone or with L-NAME in combination with sertraline. ***P 0.001 compared to L-NAME.

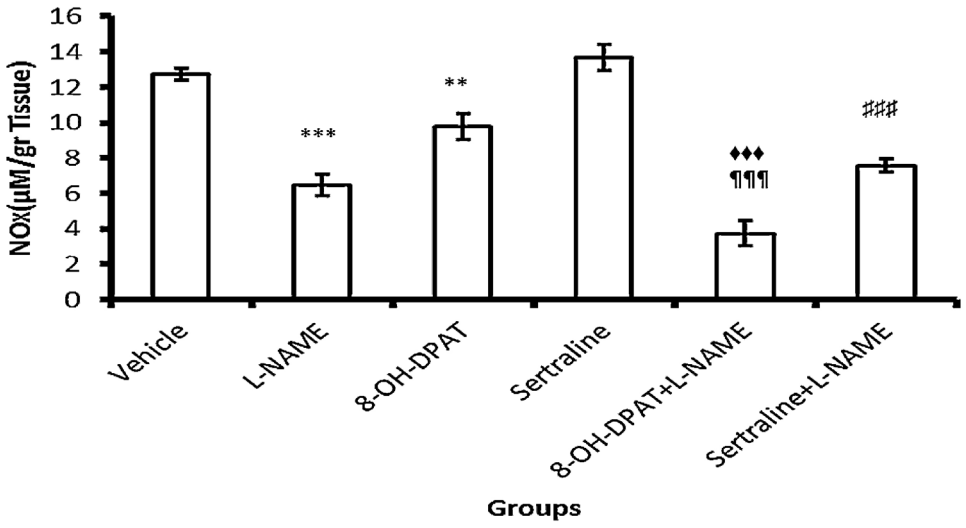

Fig. 3. The effect of the chronic L-NAME with 8-OH-DPAT or sertraline treatment on NO_X concentration. NO_X concentration was significantly reduced in pre-treatment with L-NAME in combination of 8-OH-DPAT and also this effect was observed during the treatment with L-NAME or 8-OH-DPAT alone. ***P 0.001 and **P 0.01 compared to vehicle group. ¶¶¶ $P < 0.001$ compared to 8-OH-DPAT. ◆◆◆ $P < 0.001$ compared to L-NAME. ### $P < 0.001$ compared to sertraline.

activates G protein-coupled potassium channels [40]. Although it is generally believed that the $5HT_{1A}$ activation increases the seizure threshold in most of the animal models, some studies have demonstrated that the $5TH_{1A}$ agonists such as 8OH-DPAT decrease the seizure threshold [41,42]. However, our results confirm the findings that show the $5HT_{1A}$ have anticonvulsant effect. Of course, it must be noted that 8OH-DPAT has also affinity for other $5HT_7$ receptors [19].

WAY100635 (*N*-[4-2-methoxyphenyl)-1-piperazinyl]-*N*-(2-pyridinyl)cyclo hexanecarboxamide alone had no effect on the seizure threshold. Interestingly, the co-administration of sertraline or 8-OH-DPAT with WAY-100635 further increased the seizure threshold. Similarly, Manuel-Apolinar et al. [39] reported that 8OH-DPAT increased cAMP in cortex and hippocampus and the co-administration of WAY 100635 with 8OH-DPAT produced higher levels of cAMP in these areas. They proposed a possible link among the $5HT_{1A}$ and $5HT_7$ receptors, because 8OH-DPAT had affinity to both receptors [39]. Since WAY 100635 is highly selective antagonist for the 5-HT_{1A} receptor [6], it is likely that anticonvulsant effect of sertraline and 8OH-DPAT has been potentiated by the involvement of $5HT_7$ receptor. These data suggest possible interplay between the 5-HT_{1A} and 5-HT_7 receptors during anticonvulsant drug action.

In the case of $5HT_7$, both proconvulsant and anticonvulsant effects have been reported [43–45]. According to the study of Mirski et al., the $5HT_{1/5A/7}$ agonist, 5-CT, increased the PTZ-induced seizure threshold in rats [46] and also in $5HT_7$ knockout mice, the threshold of PTZ, NMDA, cocaine and electroshock- induced seizures were decreased [44]. Thus, it is likely that the anticonvulsant effect of sertraline and 8OH-DPAT in the presence of WAY100635 has been potentiated through the modulation of $5HT_{1A}$ autoreceptors.

The effect of SSRIs partly depends on the 5-HT_{1A} auto-receptor functions. The 5-HT_7 receptors can also be involved in the therapeutic effects of these drugs. For example, SSRIs induced c-Fos expression in rats. The effect is like the 5-HT_7 receptor activation. Moreover, chronic treatment with SSRIs decreased the 5-HT_7 receptor binding [47].

The $5HT_{1A}$ receptor is widely known as an autoreceptor [40] that reduces the release of serotonin during the treatment with SSRI, and leads to a delay in the onset of therapeutic effects of SSRI. The combination of $5HT_{1A}$ receptor antagonist with the SSRI by inhibiting the autoreceptor, maximizes the serotonin levels and strengthens the effect of SSRI [15]. On the other hand, a study has shown that by a dose between 1.0 to 3.0 mg/kg of WAY100635, the somatodendritic $5HT_{1A}$ receptors have been blocked [40,42]. In the present study, this assumption may be made that the $5HT_{1A}$ antagonist (WAY100635) with preferential inhibition of autoreceptor, enhances the effect of sertraline through postsynaptic receptors. Then, increase in the amount of extracellular serotonin leads to the increase in the seizure threshold and augment the anticonvulsant effect.

NO is a free radical with signaling functions in the CNS and is mainly produced by neuronal nitric oxide synthase (nNOS) [21]. Based on previous studies, NO has both proconvulsant and anticonvulsant properties [23]. The role of nitrergic system in the central effects of 5HT agonists and SSRIs has been previously described. For example, nNOS-derived NO has been reported to induce antidepressant and anxiolytic effects [48–50]. In addition, the effects of NO on locomotor activity in the dorsal raphe nucleus is mediated through the $5HT_{1A}$ receptors [51].

In the case of epilepsy, low doses of citalopram had anticonvulsant effect through the $5HT_3$ receptors and the combination of L-NAME or 7-NI with citalopram augmented this effect [52].

In the present study, 14 days pretreatment with 8OH-DPAT, unlike sertraline, was accompanied by lower levels of NOx in brain tissues in comparison with sham-operated rats.

According to previous studies, the stimulation of $5HT_{1A}$ receptor led to downregulation of nNOS expression in the hippocampus. In addition, the knock-out of nNOS gene or use of 7-NI as a selective nNOS inhibitor, abolished anxiolytic effects of 8OH-DPAT or fluoxetine [25]. The authors suggested that nNOS was important in normal brain 5-HT function, especially in the $5HT_{1A}$ post synaptic receptor function [53]. Considering that 8OH-DPAT is a selective agonist of the $5HT_{1A}$ receptor, decreased level of NOx in 8OH-DPAT-treated rats is conceivable. WAY100635 abolished the effect of 8OH-DPAT which confirmed the involvement of $5HT_{1A}$ receptor activation. In addition, the combination of sub-effective doses of L-NAME and sertraline further decreased NOx levels and the concomitant increase of seizure threshold. Thus, it seems that interaction

between serotonergic and nitrergic system is to some extent responsible for the anticonvulsant effect of 8OH-DPAT.

Taking into account the inhibitory effect of $5HT_{1A}$ receptor agonists on nNOS, it is probable that combination of L-NAME with 8OH-DPAT augment the anticonvulsant effect of these two $5HT_{1A}$ receptor agonist. Although there are some reports that SSRIs diminish NO levels in the CNS, our results showed that sertraline did not significantly change NOx levels. Furthermore, Bahremand et al. have reported that combination of L-arginine with high doses of citalopram was mediated by 5HT3 receptor through increased activation of NOS [54]. In proof of this claim, the combination of sertraline with non-effective dose of L-NAME did not significantly change the seizure threshold or NOx levels.

5. Conclusions

During the last decade, many studies have indicated the important role of serotonin in seizure. According to the presented data, it seems that sertraline and 8OH-DPAT have anticonvulsant effect through the $5HT_{1A}$ receptors, although serotonin receptors other than $5HT_{1A}$ subtype may be involved. Furthermore, it is probable that some anticonvulsant effect of sertraline and 8OH-DPAT are through the modulation of nitrergic system.

Conflict of interest statement

None.

Acknowledgments

The authors would like to thank all who helped with this project. This study was supported by the vice chancellor of research, Kashan University of Medical Sciences, Kashan, Iran.

References

[1] Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Ann Rev Med 2009;60:355–66.
[2] Deneris ES, Wyler SC. Serotonergic transcriptional networks and potential importance to mental health. Nat Neurosci 2012;15(4):519–27.
[3] Hensler JG. Serotonergic modulation of the limbic system. Neurosci Biobehav Rev 2006;30(2):203–14.
[4] Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38(8):1083–152.
[5] Filip M, Bader M. Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system. Pharmacol Rep 2009;61(5):761–77.
[6] Aznavour N, Zimmer L. [18F]MPPF as a tool for the in vivo imaging of 5-HT1A receptors in animal and human brain. Neuropharmacology 2007;52(3):695–707.
[7] Becker A, Grecksch G, Ruthrich HL, Pohle W, Marx B, Matthies H. Kindling and its consequences on learning in rats. Behav Neural Biol 1992;57(1):37–43.
[8] Lothe A, Didelot A, Hammers A, Costes N, Saoud M, Gilliam F, et al. Comorbidity between temporal lobe epilepsy and depression: a [18F]MPPF PET study. Brain J Neurol 2008;131(Pt 10):2765–82.
[9] Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. J Neurochem 2007;100(4):857–73.
[10] Christiansen L, Tan Q, Iachina M, Bathum L, Kruse TA, McGue M, et al. Candidate gene polymorphisms in the serotonergic pathway: influence on depression symptomatology in an elderly population. Biol Psychiatry 2007;61(2):223–30.
[11] Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y. Anticonvulsant action of GBR-12909 and citalopram against acute experimentally induced limbic seizures. Neuropharmacology 2004;47(7):1053–61.
[12] Hannon J, Hoyer D. Molecular biology of 5-HT receptors. Behav Brain Res 2008;195(1):198–213.
[13] Chilmonczyk Z, Bojarski AJ, Pilc A, Sylte I. Functional selectivity and antidepressant activity of serotonin 1A receptor ligands. Int J Mol Sci 2015;16 (8):18474–506.
[14] Polter AM. Li X: 5-HT1A receptor-regulated signal transduction pathways in brain. Cell Signal 2010;22(10):1406–12.
[15] Gharedaghi MH, Seyedabadi M, Ghia JE, Dehpour AR, Rahimian R. The role of different serotonin receptor subtypes in seizure susceptibility. Exp Brain Res 2014;232(2):347–67.
[16] Pericic D, Lazic J, Jazvinscak Jembrek M, Svob Strac D. Stimulation of 5-HT 1A receptors increases the seizure threshold for picrotoxin in mice. Eur J Pharmacol 2005;527(1–3):105–10.
[17] Pericic D, Svob Strac D. The role of 5-HT(7) receptors in the control of seizures. Brain Res 2007;1141:48–55.
[18] Jakus R, Graf M, Juhasz G, Gerber K, Levay G, Halasz P, et al. 5-HT2C receptors inhibit and 5-HT1A receptors activate the generation of spike-wave discharges in a genetic rat model of absence epilepsy. Exp Neurol 2003;184(2):964–72.
[19] Lopez-Meraz ML, Gonzalez-Trujano ME, Neri-Bazan L, Hong E, Rocha LL. 5-HT1A receptor agonists modify epileptic seizures in three experimental models in rats. Neuropharmacology 2005;49(3):367–75.
[20] Obniska J, Kolaczkowski M, Bojarski AJ, Duszynska B. Synthesis, anticonvulsant activity and 5-HT1A, 5-HT2A receptor affinity of new *N*-[(4-arylpiperazin-1-yl)-alkyl] derivatives of 2-azaspiro[4.4]nonane and [4.5]decane-1, 3-dione. Eur J Med Chem 2006;41(7):874–81.
[21] Baranano DE, Ferris CD, Snyder SH. Atypical neural messengers. Trends Neurosci 2001;24(2):99–106.
[22] Dhir A, Kulkarni SK. Nitric oxide and major depression. Nitric Oxide Biol Chem 2011;24(3):125–31.
[23] Zandieh A, Maleki F, Hajimirzabeigi A, Zandieh B, Khalilzadeh O, Dehpour AR. Anticonvulsant effect of celecoxib on pentylenetetrazole-induced convulsion: modulation by NO pathway. Acta Neurobiol Exp 2010;70(4):390–7.
[24] Harkin A, Connor TJ, Burns MP, Kelly JP. Nitric oxide synthase inhibitors augment the effects of serotonin re-uptake inhibitors in the forced swimming test. Eur Neuropsychopharmacol 2004;14(4):274–81.
[25] Zhang J, Huang XY, Ye ML, Luo CX, Wu HY, Hu Y, et al. Neuronal nitric oxide synthase alteration accounts for the role of 5-HT1A receptor in modulating anxiety-related behaviors. J Neurosci 2010;30(7):2433–41.
[26] Kouchaki E, Motaghedifard M, Banafshe HR. Effect of mobile phone radiation on pentylenetetrazole-induced seizure threshold in mice. Iran J Basic Med Sci 2016;19(7):800–3.
[27] Chen HH, Chan MH. Developmental lead exposure differentially alters the susceptibility to chemoconvulsants in rats. Toxicology 2002;173(3):249–57.
[28] Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric Oxide Biol Chem 2001;5 (1):62–71.
[29] Heydari A, Norouzzadeh A, Khoshbaten A, Asgari A, Ghasemi A, Najafi S, et al. Effects of short-term and subchronic lead poisoning on nitric oxide metabolites and vascular responsiveness in rat. Toxicol Lett 2006;166(1):88–94.
[30] Mainardi P, Leonardi A, Albano C. Potentiation of brain serotonin activity may inhibit seizures, especially in drug-resistant epilepsy. Med Hypotheses 2008;70 (4):876–9.
[31] Loscher W. Preclinical assessment of proconvulsant drug activity and its relevance for predicting adverse events in humans. Eur J Pharmacol 2009;610 (1–3):1–11.
[32] Sitges M, Aldana BI, Reed RC. Effect of the anti-depressant sertraline, the novel anti-seizure drug vinpocetine and several conventional antiepileptic drugs on the epileptiform EEG activity induced by 4-aminopyridine. Neurochem Res 2016;41(6):1365–74.
[33] Sitges M, Gomez CD, Aldana BI. Sertraline reduces IL-1beta and TNF-alpha mRNA expression and overcomes their rise induced by seizures in the rat hippocampus. PLoS One 2014;9(11):e111665.
[34] Kanner AM. Depression and epilepsy: a new perspective on two closely related disorders. Epilepsy Curr Am Epilepsy Soc 2006;6(5):141–6.
[35] Thome-Souza MS, Kuczynski E, Valente KD. Sertraline and fluoxetine: safe treatments for children and adolescents with epilepsy and depression. Epilepsy Behav 2007;10(3):417–25.
[36] Sarkar S, Gangadhar S, Subramaniam E, Praharaj SK. Seizure with sertraline: is there a risk? J Neuropsychiatry Clin Neurosci 2014;26(3):E27–8.
[37] Shubrata KS, Narayanaswamy JC, Viswanath B, Rudhran V, Chandrasekhar CR, Math SB. Sertraline-induced hyponatremia and seizures in old age. J Neuropsychiatry Clin Neurosci 2012;24(1):E47.
[38] Bondarenko II, Kissin M. Use of pregabalin and sertraline in complex treatment of patients with partial epilepsy comorbid with depressive and anxiety disorders. Zh Nevrol Psikhiatr Im S S Korsakova 2012;112(5):29–36.
[39] Manuel-Apolinar L, Meneses A. 8-OH-DPAT facilitated memory consolidation and increased hippocampal and cortical cAMP production. Behav Brain Res 2004;148(1–2):179–84.
[40] Hjorth S, Westlin D, Bengtsson HJ. WAY100635-induced augmentation of the 5-HT-elevating action of citalopram: relative importance of the dose of the 5-HT1A (auto)receptor blocker versus that of the 5-HT reuptake inhibitor. Neuropharmacology 1997;36(4–5):461–5.
[41] Gerber K, Filakovszky J, Halasz P, Bagdy G. The 5-HT1A agonist 8-OH-DPAT increases the number of spike-wave discharges in a genetic rat model of absence epilepsy. Brain Res 1998;807(1–2):243–5.
[42] Invernizzi R, Bramante M, Samanin R. Role of 5-HT1A receptors in the effects of acute chronic fluoxetine on extracellular serotonin in the frontal cortex. Pharmacol Biochem Behav 1996;54(1):143–7.
[43] Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasa M, Tagashira R, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther 2010;334(1):171–81.
[44] Witkin JM, Baez M, Yu J, Barton ME, Shannon HE. Constitutive deletion of the serotonin-7 (5-HT(7)) receptor decreases electrical and chemical seizure thresholds. Epilepsy Res 2007;75(1):39–45.
[45] Yang Z, Liu X, Yin Y, Sun S, Deng X. Involvement of 5-HT(7) receptors in the pathogenesis of temporal lobe epilepsy. Eur J Pharmacol 2012;685(1–3):52–8.
[46] Mirski MA, Ziai WC, Chiang J, Hinich M, Sherman D. Anticonvulsant serotonergic and deep brain stimulation in anterior thalamus. Seizure 2009;18(1):64–70.

[47] Hedlund PB, Sutcliffe JG. Functional molecular and pharmacological advances in 5-HT7 receptor research. Trends Pharmacol Sci 2004;25(9):481–6.
[48] Miguel TT, Nunes-de-Souza RL. Anxiogenic-like effects induced by NMDA receptor activation are prevented by inhibition of neuronal nitric oxide synthase in the periaqueductal gray in mice. Brain Res 2008;1240:39–46.
[49] Workman JL, Trainor BC, Finy MS, Nelson RJ. Inhibition of neuronal nitric oxide reduces anxiety-like responses to pair housing. Behav Brain Res 2008;187(1):109–15.
[50] Zhou QG, Hu Y, Hua Y, Hu M, Luo CX, Han X, et al. Neuronal nitric oxide synthase contributes to chronic stress-induced depression by suppressing hippocampal neurogenesis. J Neurochem 2007;103(5):1843–54.
[51] Gualda LB, Martins GG, Muller B, Guimaraes FS, Oliveira RM. 5-HT1A autoreceptor modulation of locomotor activity induced by nitric oxide in the rat dorsal raphe nucleus. Braz J Med Biol Res 2011;44(4):332–6.
[52] Payandemehr B, Bahremand A, Rahimian R, Ziai P, Amouzegar A, Sharifzadeh M, et al. 5-HT(3) receptor mediates the dose-dependent effects of citalopram on pentylenetetrazole-induced clonic seizure in mice: involvement of nitric oxide. Epilepsy Res 2012;101(3):217–27.
[53] Chiavegatto S, Dawson VL, Mamounas LA, Koliatsos VE, Dawson TM, Nelson RJ. Brain serotonin dysfunction accounts for aggression in male mice lacking neuronal nitric oxide synthase. Proc Natl Acad Sci U S A 2001;98(3):1277–81.
[54] Bahremand A, Payandemehr B, Rahimian R, Ziai P, Pourmand N, Loloee S, et al. The role of 5-HT(3) receptors in the additive anticonvulsant effects of citalopram and morphine on pentylenetetrazole-induced clonic seizures in mice. Epilepsy Behav 2011;21(2):122–7.