



High-dose fluoxetine improved long-term potentiation of the hippocampal dentate gyrus in male rats

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ABSTRACT

Introduction: Paradoxical data have been reported regarding the effects of fluoxetine on different types of learning and memory. Hippocampus-dependent memory is mediated by long-term potentiation (LTP). Here, we evaluated the effects of acute administration of fluoxetine on LTP induction in the hippocampal dentate gyrus of intact rats.

Methods: Eighteen rats were divided into three groups: the control group received saline 15min before high-frequency stimulation (HFS) and the fluoxetine groups were treated with fluoxetine (2 or 10mg/kg), 15min before HFS. The rats were anesthetized with urethane and put in a stereotaxic system for surgery, electrode implantation and field recording. After ensuring a steady-state baseline response, a single intraperitoneal injection of saline or fluoxetine (2 or 10mg/kg) was done. Next, population spike amplitude, excitatory postsynaptic potential (EPSP) slope, and paired-pulse stimuli (to determine recurrent inhibitory interneuron) were measured in the hippocampal dentate gyrus in three groups.

Results: The results showed that population spike amplitude markedly increased in the fluoxetine (2 and 10mg/kg) group than in the saline group. Also, EPSP slope induction in the fluoxetine (10mg/kg) group showed an increase, 60min after HFS compared with the control group. Fluoxetine did not significantly affect recurrent inhibition.

Conclusion: These results indicated that the acute administration of high-dose fluoxetine (10mg/kg) can induce LTP. Thus, fluoxetine can be considered as a memory enhancer in intact rats.

Keywords:

Fluoxetine

Selective serotonin reuptake inhibitors

Long-term potentiation

Hippocampus

Introduction

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter, which plays a key role in modulating behavior (Bacqué-Cazenave et al., 2020; Shahidi

et al., 2018b). In the nervous system, this neurotransmitter has many functions, such as learning and memory as well as synaptic plasticity of the nervous system (Shahidi et al., 2019b). The majority of serotonin receptors

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are G protein-coupled receptors and trigger intracellular signaling cascades that can trigger long-term changes in neuronal activity resulting in behavioral changes (Catapano and Manji, 2007).

Fluoxetine, a selective serotonin reuptake inhibitor, induces a temporary rise in serotonin levels in the nervous system synapses. Environmentally relevant concentrations of antidepressants can alter intracellular signaling pathways, memory and cognitive capacity (Hamilton et al., 2016); however, major gaps still exist in our understanding of how this drug affects the brain (Keith et al., 2007). It is demonstrated that fluoxetine modulates acute and chronic psychological diseases (Kobayashi et al., 2008).

One of the most important challenges of neuroscience is to identify cellular and molecular processes underlying learning and memory formation (Lynch, 2004). Although several areas of the brain play a role in integrating multiple forms of memory, the hippocampus plays a vital role in memory formation (Molaei et al., 2020; Sa-deghian et al., 2012). Long-term potentiation (LTP) has been reported to be the most extensive memory storage mechanism in the hippocampus and neocortex (Baudry, 2001). However, for decades, the LTP memory hypothesis with conflicting evidence has remained highly controversial (Dringenberg, 2020).

There are conflicting reports on the effect of fluoxetine on memory and learning in human and laboratory animals. Fluoxetine improves learning and memory in depressed patients as well as animals (Marwari and Dawe, 2018). However, some studies have shown that fluoxetine has no effect on learning and memory in laboratory animals (Pawluski et al., 2014) and paradox reports indicated a reduction in learning and memory in fluoxetine-treated samples, including patients and experimental animals (Pawluski et al., 2014; Valluzzi and Chan, 2007). This difference may be due to variation in learning and memory or different used samples (Pawluski et al., 2014).

The effect of fluoxetine on LTP is contradictory in various studies. Some reports have stated that the fluoxetine impairs LTP in diabetic rats (Reisi et al., 2017). Also, four weeks of fluoxetine injection (0.7mg/kg) into the hippocampal CA₁ reduced LTP and increased the presence of dendritic spines (Rubio et al., 2013). However, some study showed chronic fluoxetine administration increased short- and long-term plasticity in decreased

neophobia in mice (Popova et al., 2017).

Due to the conflicting available results on the effect of fluoxetine on various forms of memory and learning as well as the lack of studies on the effect of fluoxetine on LTP in intact rats, the present study examined the effect of fluoxetine on the activity of the dentate gyrus (DG) cells using electrophysiological recording in intact rats.

Materials and methods

Animals

Eighteen adults' male Wistar rats (8 weeks old, 250±50g) were obtained from the Hamadan University of Medical Sciences. Animals were held under a 12-h light/dark period (lights on between 7:00AM and 7:00PM). Animal care, treatments, and surgery were approved by the Scientific Committees of Hamadan University of Medical Sciences (code of ethics committee: IR.UMSHA.REC.1386.53293) and conducted in accordance with the guidelines for the Care and Use of Laboratory Animals by the National Institutes of Health, USA (Publications NIH No. 85-23, amended 1985).

Rats were divided into three groups: the control group (n=6) received saline 15min before high-frequency stimulation (HFS) and the fluoxetine groups were treated with fluoxetine 2mg/kg (n=6) or 10mg/kg (n=6), 15min before HFS.

Drugs and the method of injection

Fluoxetine hydrochloride was purchased from Recordati, Italy and dissolved in saline and after a steady-state baseline response, a single injection of saline or fluoxetine (2 and 10mg/kg; intraperitoneal [IP]) was done daily. Urethane was obtained from Sigma.

Electrophysiological technique

Surgical method

Rats were anesthetized using an IP injection of urethane (1.5g/kg). Then, the skulls were fixed in a stereotaxic device and the scalp was taken. In the skull, small holes were made with the dental drill. Through pushing the skin, the skull surface was exposed and the bipolar recording electrode was placed in the granular cells of the DG (AP= -3.8mm; ML= 2.3mm; DV= 3.2mm posterior to bregma) and stimulating electrodes in the perforant pathway (PP; AP= -8.1mm; ML= 4.3mm; DV= 3.2mm posterior to bregma) were located according to the atlas of Paxinos and Watson. Using a protective heat

pad (a controlled electrical heating blanket), the animals' body temperature was maintained at $37.0 \pm 0.2^\circ\text{C}$ during operation. We used Teflon-coated bipolar wire electrodes (except for the tips) made of stainless steel ($125\mu\text{m}$ inner diameter/ $175\mu\text{m}$ external diameter, Advent Co., UK), which were inserted into the DG or PP (Lashgari et al., 2008; Shahidi et al., 2018a).

Electrophysiological recordings and LTP induction

The electrodes were lowered slowly until a positive population spike (PS) amplitude appeared with the maximum response. Single-phase square-wave pulses (0.2ms) were generated by a constant current isolation unit (A365, WPI, USA) and applied to the PP and the responses evoked in the DG. At the beginning of the experiment, an input-output curve with stimulus intensities ranging from 100 to $900\mu\text{A}$ was generated to determine the maximum PS amplitude, and then the intensity of the test stimulus was set at a level that evoked a PS amplitude of 40% of the maximum. After the final determination of electrode placement, a minimum of 30min was considered to ensure stabilization of the signal. Following baseline response recording, HFS (400kHz , stimulus duration 0.2min , 10 bursts of 20 stimuli, 10-S inter-burst interval) was performed in the PP rejoin. Then, evoked responses were noted at 5, 30, 60 and 120min after the HFS. Finally, the excitatory postsynaptic potential (EPSP) slope, PS amplitude and paired stimulation of recurrent interneurons were measured.

The PS amplitude was calculated as the difference between the initial peaks of the positive wave and the second negative wave. The EPSP slope was known to be the slope of the rising part of the first positive peak. The paired-pulse data were expressed as the ratio of the second response with respect to the first response in each sample (Karamian et al., 2015). Then, saline or fluoxetine was injected 15min before a single excitation and subsequent response from paired stimulation was recorded and their values 15min before and after the treatment were compared between three groups (Shahidi et al., 2019b).

The eTrace package (www.sciencebeam.com) was used to describe the stimulus features. Next, the potential field response was filtered (1 Hz - 3 kHz) in the DG after passing through a preamplifier for maintaining amplification ($1000\times$; DAM 80, World Precision Instruments). Representative response traces are given before

and after HFS for each group (Figure 1).

Statistical analysis

The findings are expressed as % mean \pm SEM. The experimental data were analyzed by SPSS version 16.0. PS amplitude and EPSP slope were analyzed using one-way ANOVA with Tukey's post-hoc test and recurrent inhibition of the hippocampus was assessed by paired t-test. The significance level was set at $P < 0.05$. The recurrent of hippocampal inhibitory from the second stimulation to PS amplitudes from the first stimulation.

Results

Effects of fluoxetine on PS amplitude in the dentate gyrus using 100Hz tetanic stimulation

PS amplitude exhibited a significant difference between groups. In fluoxetine (10mg/kg) group, PS amplitude increased compared with the control group 5min after HFS [$F(2,15) = 1.987$; $P < 0.05$]. Also, 30min after tetanic stimulation, PS amplitude in the fluoxetine (10mg/kg) group was higher than the fluoxetine (2mg/kg) group [$F(2,15) = 12.277$; $P < 0.001$]. Furthermore, PS amplitude in the fluoxetine (2mg/kg) group was higher than the control group 60min after titanic stimulation [$F(2,15) = 3.37$; $P < 0.05$; Figure 2].

Effects of fluoxetine on EPSP slope in the dentate gyrus using 100Hz tetanic stimulation

Comparison of EPSP slope showed that there is no meaningful difference between groups 5min [$F(2,15) = 0.215$; $P = 0.809$], 30min [$F(2,15) = 0.734$; $P = 0.496$] and 120min [$F(2,15) = 0.395$; $P = 0.68$] after tetanic stimulation. However, EPSP slope in the fluoxetine (10mg/kg) group 60min after tetanic stimulation increased compared with the control group [$F(2,15) = 0.739$; $P < 0.05$; Figure 3].

Effects of fluoxetine on the recurrent inhibition in the DG of the hippocampus

Recurrent inhibition of the hippocampal interneurons was obtained by dividing the PS amplitude of the second stimulation by the PS amplitude of the first stimulation. There was no significant difference in the recurrence inhibition before and after intraperitoneal injection at 30min after HFS (Fig. 4). Before: Saline = 50 ± 7 , Fluoxetine 2mg/kg = 52 ± 8 , Fluoxetine 10mg/kg = 54 ± 6 . After: Saline = 52 ± 9 , Fluoxetine 2mg/kg = 40 ± 9 , Fluoxetine 10mg/kg = 47 ± 9 .

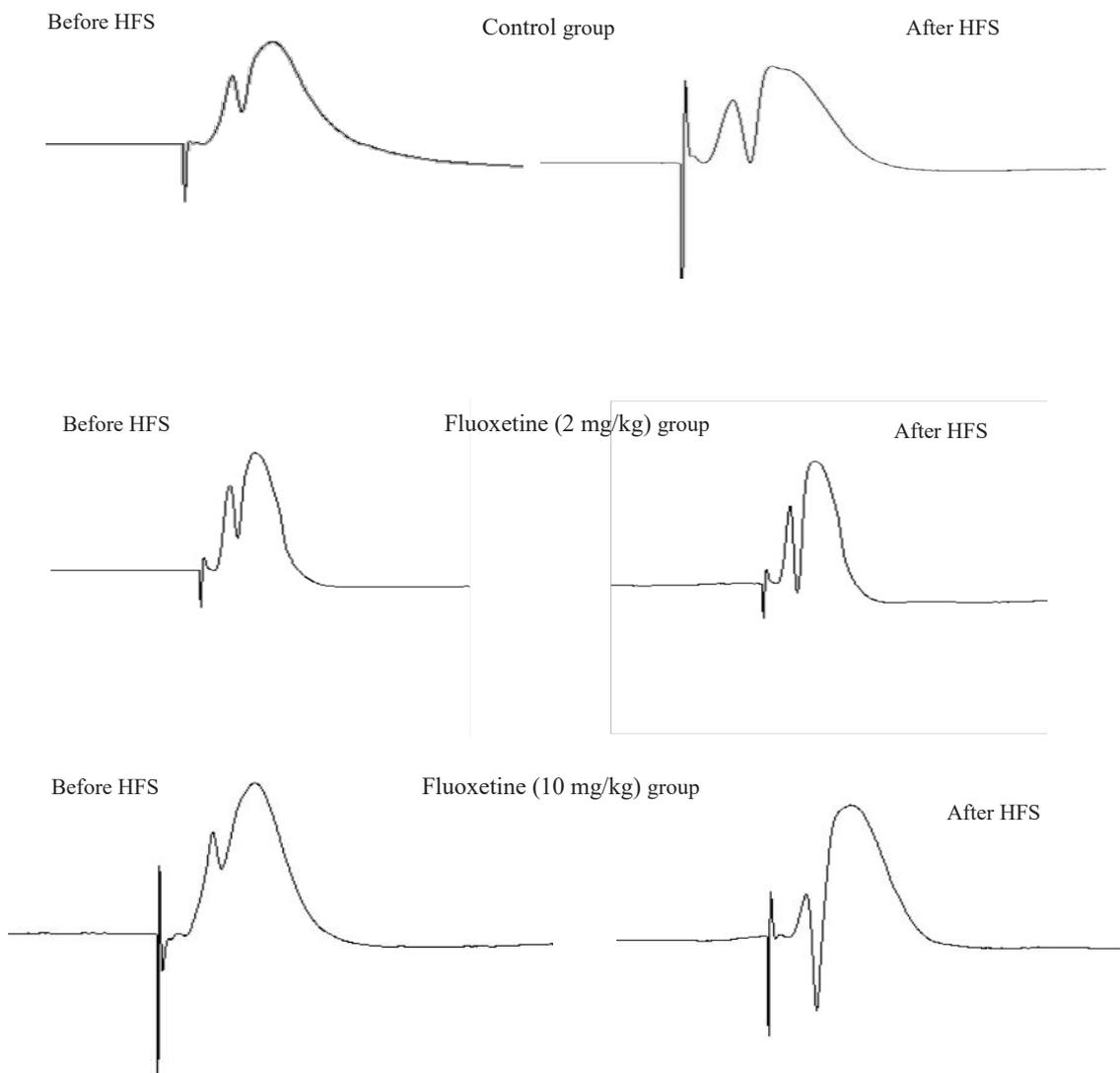


FIGURE 1. Sample traces of PS amplitude and fEPSP slope recorded in PP-DG prior to and after HFS. PS: population spike; EPSP slope: excitatory postsynaptic potential slope; PP: perforant pathway; DG: dentate gyrus; HFS: high-frequency stimulation.

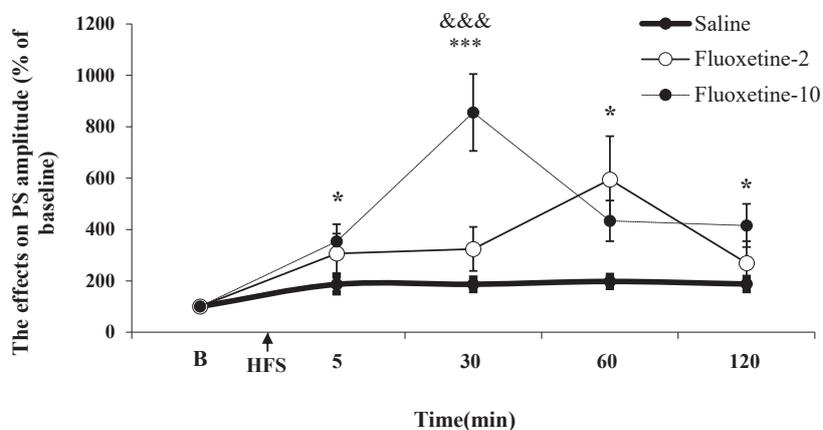


FIGURE 2. Comparison of the magnitude of PS amplitude in the dentate gyrus after administration of fluoxetine (2 and 10mg/kg; IP) or saline. At 5, 30, 60 and 120 min, the recording was done in response to stimulation following an HFS. Data are expressed as %mean±SEM. * $P < 0.05$ and ** $P < 0.01$ compared with the control group; *** $P < 0.01$ compared with the fluoxetine (2mg/kg) group (n=6). PS: population spike; high-frequency stimulation (HFS).

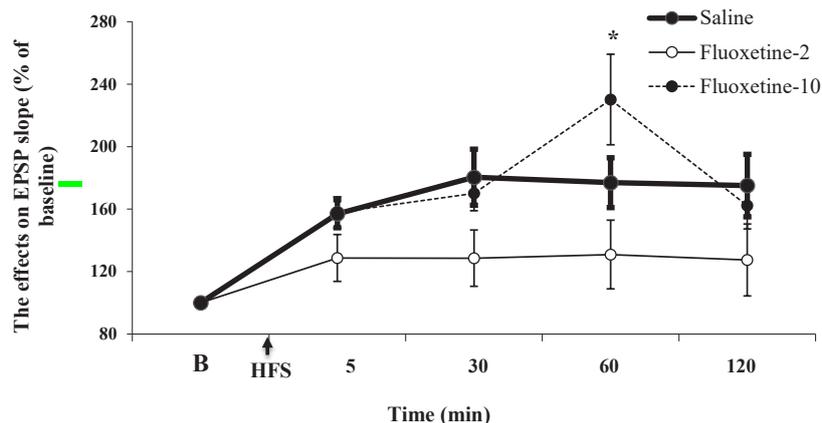


FIGURE 3. Comparison of EPSP slope before and 15min after treatment between the control and fluoxetine (2 and 10mg/kg; IP) groups in the dentate gyrus. Data are expressed as % mean±SEM (n=6). The changes in EPSP slope in each group were noted and the value of EPSP slope was considered 100% in each group. * $P < 0.05$ compared with the control group. EPSP slope: excitatory postsynaptic potential slope.

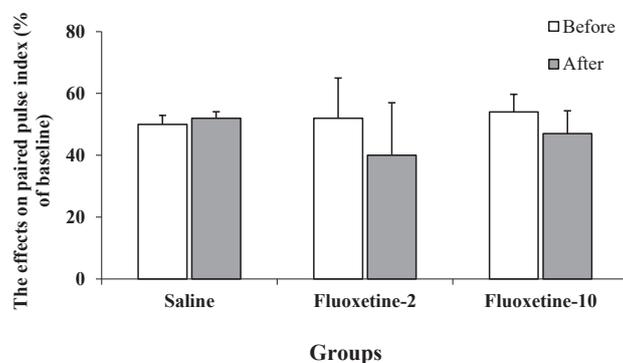


FIGURE 4. Effect of fluoxetine on recurrent inhibition of interneurons of the dentate gyrus was obtained from PS amplitude divided by the second stimulation compared with the PS amplitudes from the first stimulation. The amount of recurrent inhibition before and after injection at 30min after HFS showed no significant difference between groups.

Discussion

In the present study, the effects of acute IP administration of fluoxetine, as one of the most common selective serotonin reuptake inhibitors, were evaluated on LTP induction in hippocampal DG in intact rats. The results showed that (1) fluoxetine (2mg/kg) increased PS amplitude compared with the control group; (2) PS amplitude in the fluoxetine (10mg/kg) group was higher than in the fluoxetine (2mg/kg) group; (3) EPSP slope showed an increase in the fluoxetine (10mg/kg) group 60min after HFS compared with the control group; (4) recurrent inhibition of DG was not affected by fluoxetine.

Fluoxetine is one of the selective serotonin reuptake inhibitor antidepressants used to treat depression in particularly persistent or severe cases, and also is used for cognitive behavioral therapy (Marken and Munro, 2000). Chronic fluoxetine injection increased neurogenesis in the DG (Ohira et al., 2019).

Our results showed that the systemic administration

of fluoxetine (2 and 10mg/kg) had no effect on basal synaptic transmission in the DG. However, this drug during the tetanic excitations could modulate synaptic plasticity. Thus, both doses, particularly high-dose fluoxetine caused a larger EPSP slope and PS amplitude than the saline group 120min after HFS. Some reports have shown different effects of fluoxetine due to its interaction with different postsynaptic receptors (Meneses and Hong, 1995).

In agreement with our results, Ohashi et al. (2002) recorded that 21 days of treatment with fluvoxamine improved LTP in the hippocampal-prefrontal pathway. However, similar treatment did not affect LTP in the amygdaloid complex by stimulating the medial prefrontal cortex (Ohashi et al., 2003). In contrast to our research, *in vitro* hippocampal slices were impaired by chronic treatment with antidepressants (venlafaxine and imipramine) that prevent both serotonin and norepinephrine reuptake; this impairment is due to changes

downstream of postsynaptic depolarization and calcium influx (Cooke et al., 2014).

In addition, Stewart and Reid (2000) showed a decrease in LTP in the DG in animals that received fluoxetine for 15 days. Wang et al. (2008) stated that fluoxetine treatment decreased LTP in DG *in vitro* after 5 days of treatment; however, LTP increased after 25 days of treatment. A similar improvement of LTP was observed in the mice DG slices after 28 days of fluoxetine treatment (Bath et al., 2012). In contrast, no effect on LTP was found after 7 or 21 days of citalopram treatment; but LTP inhibition was observed 7 or 21 days of venlafaxine treatment (Cooke et al., 2009). It appears that inhibition of LTP results from increased GABA receptor function (Cooke et al., 2014).

Also, measurement of recurrent inhibition indicated the inhibition of inhibitory interneurons affecting the activity of the DG region by fluoxetine. This effect was induced by fluoxetine and was not achieved by affecting the inhibitory interneurons in the DG, but it was due to a direct effect on the PP-DG pathway.

In agreement with this study, escitalopram (a serotonin reuptake inhibitor) did not affect synaptic basal transmission in the CA₁ region of the hippocampus (Mnie-Filali et al., 2006). However, Stäubli and Xu (1995) showed that the administration of 5-HT₃ receptor antagonists, such as ondansetron significantly increased the magnitude and duration of LTP compared with the vehicle injection in the hippocampus CA₁ of free-moving rats. This difference with our results may be due to the target areas and different serotonin receptors. The results of the electrophysiological recording of 50-70% of the impaired DG region in mice showed that administration of fluoxetine (5mg/kg; for 42 days [once daily]) had no effect on the LTP induction (Keith et al., 2007). Also, another study indicated that fluoxetine could not significantly affect the activation of more cells (Keith et al., 2007). This result is not consistent with our results. Regular consumption of chronic or acute fluvoxamine, another serotonin reuptake inhibitor, could increase memory and synaptic plasticity dose-dependently in the prefrontal cortex and hippocampus, and repeated administrations were more effective and with long-term effects (Ohashi et al., 2002).

The effects of serotonin on LTP induction caused an improvement in memory and learning in biological models. Considering the dose-dependent effect ob-

served in other studies by different antidepressants, their results are consistent with our results and indicate that serotonin reuptake inhibitors at higher doses are more effective in synaptic plasticity. Therefore, fluoxetine treatment increased synaptic plasticity and dendritic spine remodeling induced the growth of cerebrocortical synapses (Rubio et al., 2013). LTP, as a form of synaptic plasticity, has been regarded as a critical cellular mechanism underlying learning and memory (Shahidi et al., 2019a).

Conclusion

Overall, our results showed that the enhancement of the activation of the serotonergic system in the DG, induced long-term potentiation, especially at higher doses. Also, LTP represents a valid molecular and cellular model for learning and memory. Thus, fluoxetine can be considered an effective agent in learning and memory.

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Conflict of interest

The authors declare no conflicts of interest.

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