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Evaluating the effect of donepezil on depression and obsessive–compulsion disorder in mice models and proposing the mechanism involved

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ABSTRACT

Introduction: Considering that donepezil (DPZ) is commonly prescribed for Alzheimer's disease patients, the aim of the present study was evaluating DPZ antidepressant effect and introducing the possible mechanism. Therefore, nicotinic (mecamylamine) and muscarinic (scopolamine) cholinergic antagonists, as well as neurosteroid sigma antagonist (progesterone) effects, were evaluated concomitantly with DPZ. **Materials and Methods:** The immobility time was measured in male mice, in the forced swimming test (FST) as a model of despair, and the number of marbles buried (MBT) in an open field was assessed as the model of obsessive–compulsive behavior in mice, the tests were verified by fluoxetine. **Results and Conclusion:** DPZ (1 mg/kg) reduced the immobility time in the FST (117 ± 4.8 s vs. control group 173 ± 3.7 s), the change was similar to fluoxetine (20 mg/kg), which reduced immobility to 52 ± 15 s. The number of marbles buried was reduced by DPZ to 50% in the MBT. Scopolamine (0.5 mg/kg) and mecamylamine (1 mg/kg) that were used concomitantly with DPZ augmented the antidepressant effects of DPZ. While high-dose progesterone (10 mg/kg) not only increased the immobility time (169 ± 7.1 s) but also reversed DPZ effects on the MBT. **Conclusion:** DPZ agonistic effects on sigma-1 receptor could be responsible for its effects on the immobility time in FST which indicates its antidepression effects. Thus, DPZ should be considered in clinical research for treating depression or obsession in patients with a history of cognition problems, or as an antidepressant in senile dementia.

INTRODUCTION

In addition to well-known symptoms of unipolar depression such as dysphoria, anhedonia, changes in appetite and weight, and sleep disorders, these patients may complain of neurocognitive disfunction for instance: Impaired thinking ability, concentration, or memory difficulties. Many studies have revealed that in individuals suffering depression memory and learning performance is also disturbed.[1,2] Brand *et al*. realized that retrieval and memorizing may be decreased in depression, particularly in the start of a task when there is a higher demand on cognitive effort.[3] Memory changes may also be present in anxiety conditions such as obsessive–compulsive disorder (OCD) patients that performed more poorly on an event-based prospective memory task.[4]

Donepezil (DPZ) is the most commonly drug administered for Alzheimer's disease (AD).[5,6] Its mechanism of action by which it affects cognition and memory performance is the inhibition of acetylcholinesterase (AchE) in the brain. Rivastigmine is a similar drug used to treat mild-to-moderate dementia in AD patients. In 2013, a 6-month observational study on 50 patients with mild AD reported that treatment with a rivastigmine patch decreased the frequency and severity of major depressive episodes.[7]

Evidently, a complex set of neurotransmitters contributes to the mechanism of depression. For half a century, the majority of researchers have explained depression with the monoamine hypothesis, which suggests that low levels of brain monoamines, such as serotonin, noradrenaline, and

dopamine, are responsible for the development of symptoms. Although using antidepressant drugs, the effect on the monoaminergic system is acute, the mood improving the effect of these medications take several weeks to become noticeable.[8] Therefore, the monoamine hypothesis has not been successful to thoroughly explain the nature of despair.[9] It was also proposed that central cholinergic activation could inhibit depression, while anticholinergic drugs or adrenergic stimulation-induced behavioral activation and arousal.[10]

Recently, there has been more attention on sigma receptors as target of drug development related to mental disorders such as depression, AD, and schizophrenia.[11] The sigma-1 receptor is a 223 amino acid protein with two transmembrane domains. Sigma-1 receptors mainly reside on the endoplasmic reticulum (ER), and they dynamically translocate inside cells. Further studies revealed that sigma-1 receptors are particularly enriched at the mitochondria-associated ER membrane. It has been proposed that sigma-1 receptors function as "receptor chaperones."[12] In the steady state, sigma-1 receptors form a complex that is inhibited from activation. A decrease of Ca2+ in the ER causes the sigma-1 receptor to separate from the complex, and thus the sigma-1 receptor becomes an activated chaperone. The activated sigma-1 receptor then binds to the inositol triphosphate receptor. As a result, Ca2+ flows into the mitochondria through voltage-dependent anion channels. This inflow of Ca2+ finally results in neuroprotection and neurite outgrowth.[13] Evidently, sigma-1 receptor stimulation decreased immobility in animal models of despair; in both tail suspension test and forced swimming test (FST).[13,14] Sigma-1 receptors may also play an important role in antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and fluvoxamine[15] as well as venlafaxine.[16] Researchers have also shown that the release of dopamine in the brain of rodents was altered by administration of sigma receptor agonists.[17,18]

Neurosteroids interaction with sigma-1 receptors was first advocated in 1988.[19] Neuromodulatory actions of neurosteroids include nuclear and non-nuclear effects; the second action is apparently related with sigma-1 receptors. Progesterone was the most potent inhibitor of sigma-1 specific radioligand binding; among the steroids that were verified. In many experiments, progesterone behaved like other known sigma-1 antagonists, and pregnenolone sulfate acts as other known sigma-1 agonists.[20] It has been reported that DPZ binds to sigma receptors in the brain.[21] On the basis of these evidence and previous experiments that proved the antidepressant effects of rivastigmine on animal model of despair,[22] the following study was designed.

Until now, there is no evidence of the possible antidepressant effects of DPZ, and the possible mechanism involved. Perhaps, these drugs could be useful in depression patients suffering from memory problems. Thus, the aim was to evaluate the antidepressant, antiobsession effects of DPZ in mice. As DPZ has proven sigma-1 receptor agonist effects, we further analyzed its antidepressant effects while coadministered with a sigma-1 receptor neurosteroids antagonist, progesterone. The main action of DPZ as previously noted is AchE inhibition, thus change in the cholinergic function could also be involved in its antidepressant effects this was evaluated by coadministrating it with scopolamine; a centrally acting inhibitor of the muscarinic cholinergic receptor, mecamylamine; nicotinic cholinergic receptor antagonist.

MATERIALS AND METHODS

Animals

Male albino mice weighing 28 ± 3 g were housed in cages, six animal in each cage at 21°C ± 2°C in a 12 h light-dark cycle (the lights were on from 6 am to 6 pm). Tap water and standard food pellets were available *ad libitum*. Tests were performed only after the mice had acclimated to the above environment for at least 2 days. All the experiments were done between 08:00 and 13:00 h, to minimize circadian rhythm influence in the pharmacology behavior laboratory. All animal procedures were performed in accordance with guidelines for the Care and Use of Laboratory Animals issued by Isfahan University of Medical Sciences (Ethical No: IR.MUI.REC.1394.3.696).

Marble Burying Test (MBT)

This is a method used to evaluate anxiety behavior, OCD. With minor modification from method presented by Njunge 1991, mice were placed individually in polypropylene cages (42 cm × 24 cm × 12 cm) containing 12 clean glass marbles (1 cm diameter) evenly spaced on 5 cm deep sawdust without food or water. The number of marbles at least two-thirds buried was counted after10, 20, and 30 min.[23]

Forced Swimming Test (FST)

With a few modifications, mice were forced to swim for 6 min in water of 25°C in a glass beaker (diameter 12.5 cm). The depth was about 12 cm, thus the mice could not touch the bottom of the glass beaker with their paws or tail, and they could not escape. After 6 min, the mice were dried carefully and returned to their home cage. Immobility time was recorded in the last 4 min, defined as the time spent while animal was floating staying still or using righting movements. Swimming was defined as horizontal movements which involved at least two limbs.[24] Each animal was first subjected to MBT for 30 min and then tested in the FST.

Drug Therapy

DPZ (Sigma-Aldrich, Germany) 1 mg/kg body weight,[25] scopolamine (Tehran-shimi, Iran) 0.5 mg/kg, mecamylamine hydrochloride (Sigma-Aldrich, Germany) 1 mg/kg,[22] and fluoxetine HCl 20 mg/kg (a gift from Pars Daru, Iran) as the positive control were used, these drugs were diluted in normal saline. Progesterone (Iran hormone, Iran) 10 mg/kg[26] was diluted in normal saline solution containing 0.1% Tween 80, thus the control group received appropriate vehicle solution. The drugs administered with DPZ were injected at 10 min interval and all injections were intraperituneally, MBT was performed 30 min after DPZ administration. All animals were injected 10 ml/kg according to their body weights.

Data Processing and Statistical Analysis

Results were expressed as group mean ± standard error of the mean. All results were analyzed by one-way analysis of variance, followed by Tukey's multiple comparison tests,

p<0.05 was considered significant. The GraphPad Prism 6 software was used for data analyzing and making graphs.

RESULTS

The Effect of Drugs on Animal Performance in the FST

The immobility time was reduced in the FST by DPZ (117 ± 4.8 s vs. control group 173 ± 3.7 s, $P < 0.01$). As it is shown in Figure 1a, scopolamine decreased the immobility time which indicated the improvement of despair behavior in the animals (106 ± 13 s, $P < 0.01$). Mecamylamine alone decreased immobility although it was not significant compared with the control group (128 ± 8.8 s). The immobility time in FST was increased by progesterone (184 ± 13 s) indicating that it induces depressive behavior.

As it is demonstrated in Figure 1b, the coadministration of DPZ with mecamylamine or scopolamine both caused a greater decrease in the immobility time (93 ± 4.9 s and 65 ± 3.5 s, respectively, $P < 0.001$ vs. DPZ + vehicle 132 ± 3 s). Although immobility time was increased significantly when progesterone was coadministered with DPZ, it reversed the beneficial effects of DPZ on depressive behavior (169 ± 7.1 s, $P < 0.001$ vs. DPZ + vehicle).

The Effect of Drugs on Animal MBT Behavior

The number of marbles buried was counted each 10 min for half an hour to assess animal obsession behavior. Figure 2a shows that after 20 min DPZ has significantly reduced the number of marbles buried (2 ± 0.4 vs. 3.7 ± 0.3 control). After 30 min, the difference was even more noticeable (3 ± 0.5 vs. 6.6 ± 0.3 control, $P < 0.001$). These changes were parallel with our reference drug fluoxetine. Scopolamine-treated animals after 30 min buried obviously more marbles compared to control animals (9 ± 0.6, $P < 0.01$).

Figure 2b shows that mecamylamine used together with DPZ significantly increased the number of marbles buried after 20 min (3.7 ± 0.3 vs. 2 ± 0.4 its corresponding control group, $P < 0.05$). This value rose even higher after 30 min (5 ± 0.2 vs. 3 ± 0.5, $P < 0.01$). Scopolamine coadministration with DPZ increased the number of buried marbles only after 30 min (4.7 ± 0.3, $P < 0.05$). Progesterone administered concomitantly with DPZ significantly increased the number of marbles buried after 20 and 30 min (4.5 ± 0.5 and 7.5 ± 0.5, respectively, $P < 0.001$) compared to the DPZ + vehicle group.

DISCUSSION

According to our experiments, DPZ reduced the immobility time in the FST model of despair that presented its possible antidepressant effects. It also reduced the number of marbles buried in MBT which indicated the drug could also alleviate obsession behavior. To verify the FST and MBT experiments, fluoxetine (SSRI antidepressant) was used and it significantly reduced immobility and marble burying behavior.

There are reports indicating that AD patients treated with rivastigmine showed reversal in depression which was evaluated by the Hamilton depression scale.[27] Animal studies also proved antidepressant effects of rivastigmine in the tail suspension test and olfactory bulbectomized mice.[22,28] It was determined that rivastigmine not only enhances the cholinergic system but also repairs serotonergic system of the hippocampal, which improves depressive behaviors.[28] Therefore, other mechanisms must be considered in antidepressant effects of AchE inhibitors. According to our results, DPZ could have a similar impact on depression as rivastigmine that could be connected to the cholinergic system.

Scopolamine as a competitive muscarinic receptor antagonist acting centrally also showed beneficial effects on despair. This is in connection to a previous systematic review indicating that scopolamine is an efficient antidepressant and shows its effects on depression as fast as 3 days.[29] Using scopolamine together with DPZ augmented the beneficial

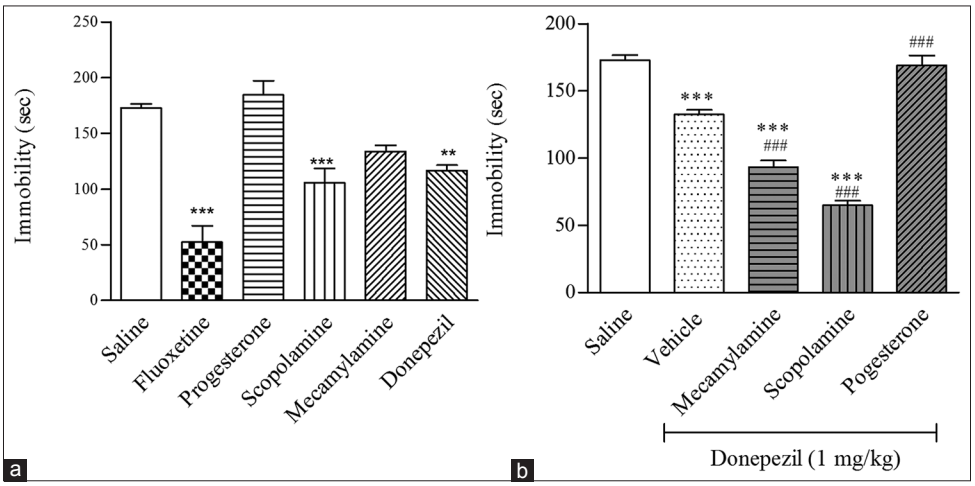

Figure 1: The effect of treatments alone (a) or in combination (b) with donepezil on depressive performance in the forced swimming test. The immobility time is the total time animals were immobile during the last 4 min of the total 6 min test. Number of animals in each group was 6. The drugs were injected ip; scopolamine 0.5 mg/kg, mecamylamine 1 mg/kg, progesterone 10 mg/kg, and fluoxetine 20 mg/kg. Results are expressed as group mean ± standard error of the mean and analyzed by analysis of variance followed by Tukey's comparison tests. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with saline group. $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ compared with vehicle

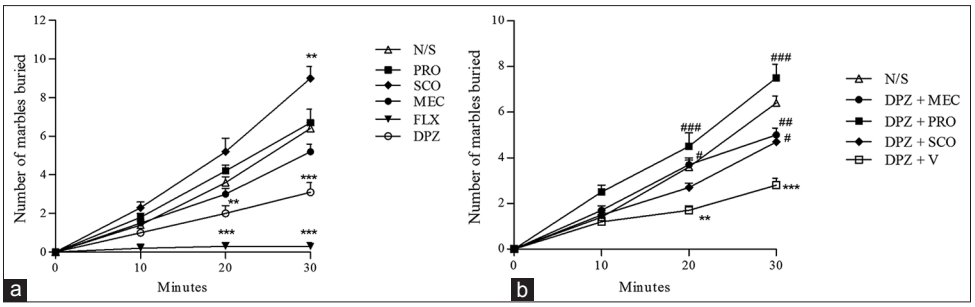

Figure 2: The effect of each drug alone (a) and in combination (b) with donepezil in the marble burying test. The number of marbles at least two-thirds buried with sawdust was counted after 10, 20, and 30 min. Number of animals in each group was 6. Results are expressed as group mean ± standard error of the mean and analyzed by analysis of variance followed by Tukey's comparison tests. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with normal saline (N/S). $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with DPZ + vehicle. DPZ: Donepezil, MEC: Mecamylamine, PRO: Progesterone, SCO: Scopolamine, V: Vehicle

effects on despair. Inhibiting the muscarinic receptors with scopolamine simultaneously with DPZ was effective to decrease immobility in FST. The antidepressant effects might be because of increased Ach effects on the nicotinic cholinergic receptors or because of the DPZ agonist effect itself on other receptors. Mecamylamine, nicotinic receptor antagonist, on its own did not have beneficial effects on despair in the FST; this was also seen in our previous studies in the tail suspension test.[22] However, using it concomitantly with DPZ, it did not reverse DPZ beneficial effects on immobility time, and it improved the antidepressant effects of DPZ. These findings are supported by the previous research indicating that augmented Ach signaling in humans causes an increased in depressive symptoms.[30] This was observed following administrating the AChE blocker physostigmine, to patients with depression history, apparently through increased central acetylcholine levels.[30] Therefore, inhibiting nicotinic or muscarinic receptors while using DPZ increased its antidepressant effects, supporting the fact that other receptors are involved in its antidepressant effects.

Evidently, DPZ is a sigma receptor agonist.[21] Recently, sigma-1 receptor has gained attention for possible relation to depression or anxiety-related behavior.[31,32] Distinct chemically, sigma-1 receptor agonists such as (+)-pentazocine, 1,3-di-o-tolyguanidine, SA-4503, dextromethorphan igmesine, and many others, dose-dependently reduce immobility in animal models of depression, including FST; their antidepressant action was reversed by the selective sigma-1 receptor antagonist NE-100.[33,34] Progesterone has been used in various studies as a sigma receptor antagonist.[16,35] Neurosteroids have recently gained attention as the most possible endogenous sigma-1 receptor ligands.[36] Sigma-1 receptors present new progesterone membrane targets, progesterone inhibits voltage-gated ion channel modulated by sigma receptor, and this action of progesterone may be responsible for changes in cardiovascular and brain function during endocrine changes.[35] This effect of progesterone was also confirmed in our study, the beneficial effects of DPZ on the immobility time in FST were only antagonized by progesterone. Although molecular studies were not included in our study, it could be interpreted that the antidepressant effect of DPZ is related to its sigma receptor agonistic effect, and further studies in this regard are warranted. Last but not least is the beneficial effect of DPZ on MBT, which was similar to fluoxetine. The animals buried less marble after 30 min, thus it was concluded that DPZ has beneficial effects on OC behavior in mice. Since this effect was significantly antagonized by progesterone, it could be deduced that sigma-1 receptors had played an important role. It has been reported that rats and mice bury marbles, and this behavior is diminished by low doses of anxiolytic drugs.[23] Compounds active on 5-HT systems that relieve anxiety, depression, or OCD, also inhibited marble burying behavior.[37,38] As we have examined previously, this method is a reliable method to predict the beneficial of experimental drugs on OCD.[39] It does not seem that marble burying mice are anxious they are not intentionally burying the marbles, but they simply fall through the bedding after it is dug.[40] Therefore, MB measures digging behavior which is partially dependent on hippocampal function.[41] On the basis of our studies, this is only a hypothesis which opens new trends toward research regarding DPZ effects on depression and OCD considering its agonistic effects on sigma-1 receptors. Another benefit of the MBT test was to analyze animals' normal movements, to separate immobility in the FST from sedative behavior. According to our test, all the animals showed normal animal activity in the open field.

To sum up, DPZ as a sigma-1 receptor agonist could be promising in treating depression or OCD in patients with a history of cognition problems. Thus, DPZ should be a candidate for further clinical research in individuals suffering from affective disorders and history of cognition problems, or as an antidepressant in senile dementia.

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