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HEALTH SCIENCES

Effects of mirabegron on depression, anxiety, learning and memory in mice

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Abstract: Mirabegron is the first b3-adrenoceptor agonist to enter clinical practice and has been approved for the treatment of symptoms of OAB. The aim of this study is to investigate whether the mirabegron has an effect on depression, anxiety, learning, and memory. We investigated the effects of mirabegron on depression, anxiety, learning and memory by using forced swimming test, elevated plus maze test, passive avoidance and Morris water maze in mice. Imipramine and mirabegron (3, 6 and 9 mg/kg) significantly reduced immobility time in forced swimming test. Diazepam and mirabegron (3, 6 and 9 mg/kg) significantly increased the time spent in open arms and the number of entries to the open arms in elevated plus maze test. Furthermore, cognitive performance impaired with scopolamine has been significantly improved with 9 mg/kg mirabegron. Mirabegron (6 and 9 mg/kg) significantly increased the time spent in the target quadrant in naive mice. While scopolamine significantly increased the swimming speed, mirabegron (9 mg/kg) significantly decreased the swimming speed in scopolamine-treated mice. Mirabegron might be clinically useful for the treatment of OAB in elderly patients that should use drugs against depression and anxiety, without disrupt learning and memory.

Key words: Mirabegron, depression, anxiety, learning, memory, mice.

INTRODUCTION

Overactive bladder (OAB) is a condition that is characterized by involuntary contraction of the muscle in the wall of the urinary bladder. The exact cause of these contractions is often not known. Millions of people around the world are affected from this and struggle with OAB symptoms. Patients with OAB may feel embarrassed, isolate themselves, or limit their work and social life. Due to emotional distress, anxiety, depression, sleep disturbances and issues with sexuality, OAB can affect their life qualities (Lee et al. 2015, Coyne et al. 2004). Depression and anxiety are associated with OAB and their levels are mainly related with urgency incontinence and nocturia (Melotti et al. 2018).

There are various behavioral interventions such as regulating fluid intake, timed voiding and bladder holding techniques using pelvic floor in the management of OAB. Ifthese behavioral interventions do not adequately help with the symptoms of OAB, treatments with certain medications can also be used. To suppress smooth muscle contractions and increase capacity of bladder, anticholinergics such as oxybutynin, tolterodine, darifenacin, solifenacin and fesoterodine are first-line agents used for the treatment of OAB (Glavind & Chancellor 2011). On the other hand, Anticholinergics may cause more side effects than the other drugs and worsen symptoms of dementia in elderly

patients. Mirabegron (YM178) is a noveleffective and safe beta 3-adrenergic receptor agonist used in patients with OAB. It is known to cause relaxation of the bladder and and increase its capacity. It is well tolerated overall, with a lower incidence of side effects than that of antimuscarinics drugs (Kelleher et al. 2018).

The role of beta 3-adrenergic receptor agonist in regulating lipolysis has been well known for a long time. Furthermore, beta 3-adrenergic receptor agonist has been shown to be found in non-adipose tissues including hearth, vessels, brain, liver, lung and kidney (Coman et al. 2009). Deficiencies of serotonergic system are likely involved in the pathogenesis of both depression and anxiety. Activation of beta 3-adrenergic receptor by agonist has been revealed to increase brain tryptophan levels and serotonin synthesis in rodent brain (Lenard et al. 2003). This result indicated that beta 3-adrenergic receptor may modulate serotonergic transmission in the brain. Again, in our previous studies, we showed that the anxiolytic and antidepressant-like effects of amibegron (beta 3-adrenergic receptor agonist) may be mediated by an interaction with serotonin 5-HT1A, serotonin 5-HT2A-2C and serotonin 5-HT3 receptors (Tanyeri et al. 2013a, b).

Use of medicines in an unapproved indication, age group, dose or administration route is defined as off-label drug use. Although there are negative aspects of off-label drug use, there are various positive aspects. Off label drug use provides new opportunities for existing approved drugs, and reduces the time and cost involved in drug discovery with respect to traditional drug development method. The aim of present study is to investigate the effects of mirabegron on depression, anxiety, learning and memory to understand if mirabegron may be effective in OAB caused mood and cognitive disorders.

MATERIALS AND METHODS

Animals

One hundred eighty six male inbred BALB/c ByJ mice (Animal Research Center, Sakarya-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. Since female animals mostly don't be used in behavioral tests because they have menstrual cycle which may cause wrong positive or negative results.We used male animals similar to our previous studies (Tanyeri et al. 2013a, b). Animals (4–5 per cage) were kept in the laboratory at 21 ± 1.5 °C with 60% relative humidity under a 12 h light/dark cycle (light on at 8.00 p.m.). Tap water and food pellets were available ad libitum. All procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Sakarya University Ethics Committee (04.04.2018, Number = 12, Sakarya/Turkey).

Drugs

Mirabegron was obtained from Astellas (Turkey). Imipramine hydrochloride, diazepam and scopolamine were purchased from Sigma Chemicals (St Louis, Mo, USA). Drugs were dissolved in saline. Saline was used as the vehicle controls. All the drugs were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. The doses were chosen based on previous behavioural studies (Sawada et al. 2013, Ulak et al. 2010). Drugs were prepared freshly on the day of experiment.

Experimental Design

We investigated the effects of mirabegron on depression, anxiety, learning and memory by

using forced swimming test, elevated plus maze test, passive avoidance andmorris water maze, respectively, in mice. Additionally, the locomotor activity was evaluated by measuring the total distance traveled in the open field test.

Forced swimming test (FST)

FST was performed which was described by Porsolt et al. (1977, 1978). Briefly, the mice were dropped individually into plexiglas cylinders (height 25 cm, diameter 10 cm) containing 10 cm of water maintained at 23-25°C and left there for 6 min. The duration of immobility (in seconds) was recorded during the last 4 min of the 6-min testing period. The absence of hind leg movement was recorded as immobility by stopwatch cumulation by a single observer who was aware of the treatments during the exposures.

One hundred eighty six male inbred BALB/c ByJ mice were used in the Forced Swimming Test. Mice were randomly divided into experimental groups (n=8-10 mice): saline, imipramine 30 mg/kg (Imip), mirabegron 3, 6 and 9 mg/kg, respectively. All experiments were performed between 10.00 and 12:00 a.m. All drugs or saline were given 30 min before the experiment.

Elevated Plus-Maze (EPM) Test

Anxiety-related behavior was measured by the EPM test. The experiments were conducted in a dimly lit, semi-soundproof room, illuminated with table lamp (80 lux). Maze was made of wood and consisted of two open (29 cm long × 5 cm wide) and closed arms(29 cm × 5 cm with 15 cm high walls) forming a square cross with a 5 cm square center piece.In order to avoid falls the open arms was surrounded by a short (1 cm) plexiglass edge. The maze was elevated 40 cm above the floor. The open arms and central platform were painted white and enclosed arms were painted black.

Each mouse was placed at the center of the maze facing one of the open arms and allowed to explore the maze. During a 5-min test period, the number of entries into both open and enclosed arms of the maze (defined as the entry of all four limbs into the arms) and the time spent in the open arms was recorded. The observer was present always in the same position towards to the open arms and behind the animals. The open arm activity wasevaluated as the following: 1) time spent in the open arms relative to the total time spent inthe plus-maze (300 s), expressed as a percentage; 2) number of entries into the open arms relative to the total number of entries into both the open and closed arms, expressed as a percentage. These values were used as indices of anxiety in mice. Any animal that fell off the maze was excluded from the experiment.

Elevated plus-maze is one of the tests used to evaluate anxiety in animals. In the normal cases, the animals prefer to stay within the closed arms instead of open arms owing to feel more safe. Drugs with anxiolytic properties increase the time spent on the open arm. As the values for both of the measured parameters changed in the same direction compared to control values (i.e., if both the time spent in the open arms and the number of open arm entrieswas increased or if both were decreased) and the change in one of the parameters was statistically significant, then an effect on anxiety was considered to have occurred. The time spent in the open arms and the numbers of open arm entries were always observed to change in the same direction.

Forty one male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in EPM: saline, diazepam 2 mg/kg (Dzm), Mir-3, Mir-6 and Mir-9. Each experimental group consisted of 7-10 mice. All experiments were performed between 10.00

and 12:00 a.m. All drugs or saline were given 30 min before the experiment.

Passive Avoidance (PA) test

Animals were trained in a one-trial, step-through PA apparatus to evaluate memory based on contextual fear conditioning and instrumental learning. A decrease in retention latency indicates an impairment in memory in the PA task. The apparatus consisted of a box with an illuminated part (L 7 × 12.5 × h 14 cm) and a dark part (L 24 × 12.5 × h 14 cm), both equipped with a grid floor composed of steel bars (0.3 cm diameter) spaced 0.9 cm apart. The inhibitory avoidance task consisted of two trials. On the first day of training, the mice were individually placed into the light compartment and allowed to explore the boxes. The intercompartment door was opened after a 10 second acclimation period. In the acquisition trial, each mouse was placed in the illuminated compartment, which was lit by a bright bulb (2000 lux). If the mouse stepped into the dark compartment (2/3 of the tail in the dark compartment), the door was closed by the experimenter, and an inescapable foot shock (0.3 mA/1 second) was delivered through the grid floor of the dark compartment. A cut-off time of five minutes was selected. The time taken to enter the dark compartment (training latency) was recorded. Immediately after the shock, the mouse was returned to the home cage. The retention trial started 24 hours after the end of the acquisition trial. The animals received drugs prior to retention training. Each mouse was placed in the illuminated compartment as in the training trial. The door was opened after a 10 second acclimation period. The step-through latency in the retention trial (with a maximum 300 seconds cut-off time) was used as the index of retention of the learned experience. A shock was not applied during the retentiontrial.

Forty eight male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in PA test: saline; scopolamine 0,6 mg/kg (Scop), Mir-3, Mir-6 and Mir-9 and Scop +Mir-9. Each experimental group consisted of 8 mice. All experiments were performed between 10.00 and 12:00 a.m.. All drugs or saline were given 30 min before the experiment.

Morris Water Maze (MWM) test

The MWM comprised a circular pool (90 cm diameter) filled with water (22°C) and rendered opaque by addition of small black balls. The pool was located in a dimly lit, soundproof test room with various visual cues, including a white/ black colored poster on the wall, a halogen lamp, a camera, and the experimenter. The maze was divided into four quadrants, and three equally spaced points served as starting positions around the edge of the pool. The order of the release positions was varied systematically throughout the experiment. A circular escape platform (6 cm diameter and 12 cm high) was located in one quadrant 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions. Video tracking was conducted with a video camera focused on the full diameter of the pool. Navigation parameters were analyzed using the Ethovision 8.5 video analysis system (Noldus Ethovision XT). Mice were trained in MWM five times per day (familiarization session, S1, S2, S3, and S4). One familiarization and four acquisition sessions were carried out using the MWM. During the familiarization session and acquisition phase of experiment, each mouse underwent three trials. The delay between trials was 60 seconds, and a 1-day interval was used between each session. For each trial, the mouse was removed from the home cage and placed in the water maze at one

of three randomly determined locations with its head facing the center of the water maze. After the mouse had found and climbed onto the platform, the trial was terminated and the escape latency was recorded. If the mouse did not climb onto the platform in 60 seconds, the trial was terminated, and experimenter guided the mouse to the platform; an escape latency of 60 seconds was recorded. Twenty-four hours after the final acquisition session, a "probe trial" was used to assess the spatial memory retention of the location of the hidden platform. During this trial, the platform was removed from the maze and the mouse was allowed to search the pool for60 seconds. The percent of time spent in each quadrant was recorded.

Fifty three male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in MWM test: saline; scopolamine 0,6 mg/kg; mirabegron 3 mg/kg; mirabegron 6 mg/kg; mirabegron 9 mg/kg; scopolamine 0,6mg/kg+mirabegron 9 mg/kg. Each experimental group consisted of 8-10 mice. All experiments were performed between 10.00 and 12:00 a.m.. All drugs or saline were given 30 min before the probe trial of MWM test.

Open field test

Since compounds altering motor activity may give false positive/negative effects in FST, elevated plus maze test, passive avoidance test and morris water maze test, spontaneous locomotor activity of mice was evaluated by monitoring the activity of the animals in an open field. The animals were placed in the center of the apparatus and behaviors were recorded for a period of 5 min using the Ethovision-XT video tracking system. The locomotor activity was evaluated by measuring the total distance traveled in the apparatus and the speed of the animals.

Statistics

Data were expressed as mean±SEM. The statistical analysis (InStat Statistical Software Program) was performed using one-way or two-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $P<0.05$ was considered as statistically significant.

RESULTS

Forced Swimming Test

One-way ANOVA showed a significant effect of mirabegron and imipramine treatment upon immobility time in FST [$F(4.44)=55,650$, $p<0.0001$]. Post-hoc comparisons revealed that imipramine and all doses of mirabegron significantly reduced immobility time, compared to saline group ($p<0.001$; Fig. 1). Additionally, there was a significant difference between imipramine and all doses of mirabegron.

Elevated Plus Maze Test

One-way ANOVA showed a significant effect of drug treatment upon the time spent staying in open arms in EPM test [$F(4, 41)=14,646$, $p<0.0001$; Fig. 2a]. Post-hoc comparisons revealed that diazepam (2 mg/kg) significantly increased the time spent in open arms compared to saline group ($p<0.001$) and also mirabegron (3, 6 and 9 mg/kg) prolonged the time spent in open arms ($p< 0.05$, $p< 0.01$ and $p< 0.001$ respectively) (Fig 2a).

One-way ANOVA displayed an important effect of drug treatment upon the number of entries to the open arms in EPM test [$F(4,41)=17,575$, $p<0.0001$; Fig. 2b]. Post-hoc comparisons revealed that diazepam (2 mg/kg) significantly increased the number of entries to the open arms compared to saline group ($p<0.001$). Mirabegron (3 mg/kg) did not have any effect on the number of entries into the

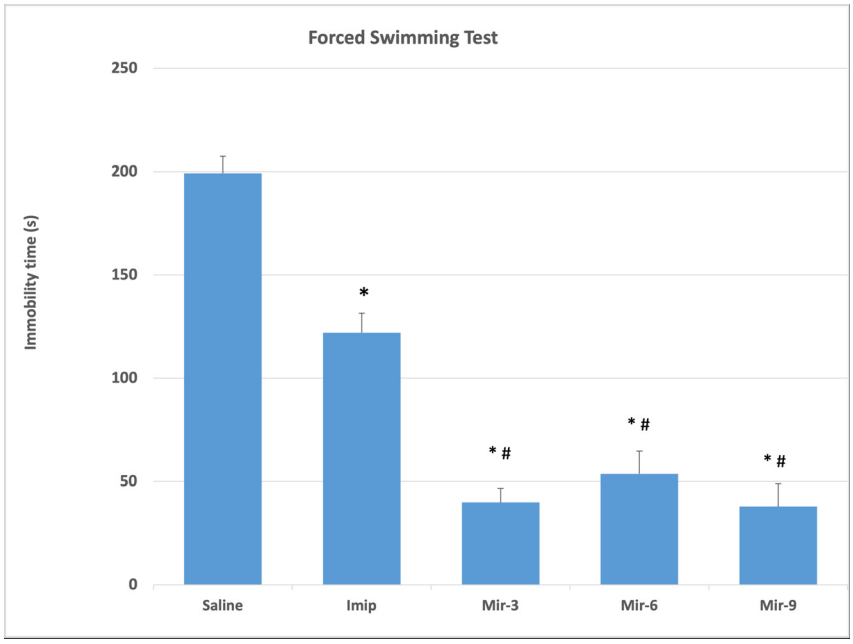

Figure 1. Immobility time (in seconds) in the forced swim test. Data were expressed as mean±SEM. (Saline (n=9); Imip 30 mg/kg (n=8); Mir 3 mg/kg (n=9); Mir 6 mg/kg (n=8); Mir9 mg/kg (n=10). *: $p<0.001$ compared to Saline group, by ANOVA (Tukey test)#: $p<0.001$ compared to Imip group, by ANOVA (Tukey test).

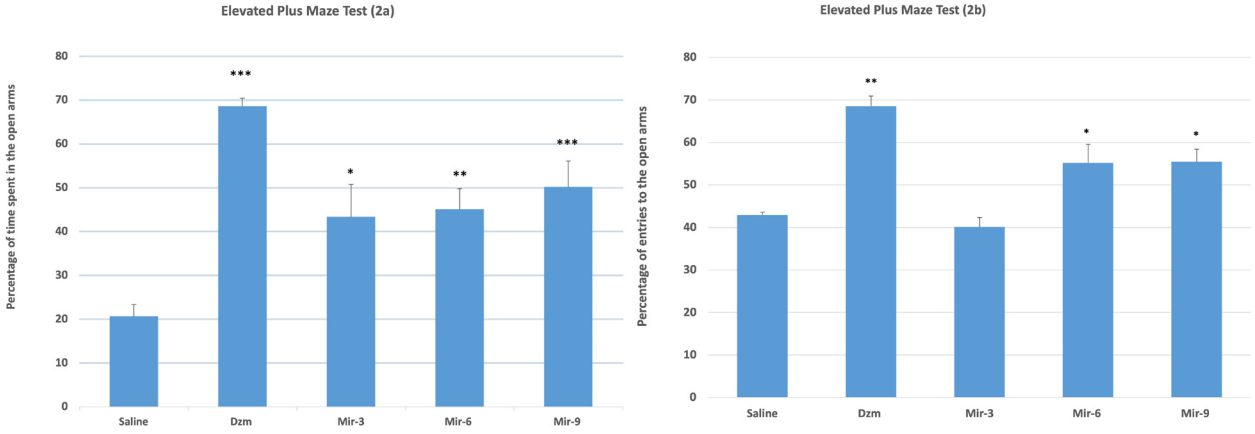

Figure 2. Percentage of time spent in the open arms (2a) and percentage of number of entriesto the open arms (2b) in elevated plus-maze test. Data were expressed as mean±SEM; (Saline(n=8); (Dzm 2 mg/kg (n=10); Mir 3 mg/kg (n=7); Mir 6 mg/kg (n=8); Mir 9 mg/kg (n=8). *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ compared to Saline group, by ANOVA (Tukey test).

open arms while mirabegron (6 and 9 mg/kg) increased the number of entries into the open arms ($p< 0.05$ and $p< 0.05$, respectively) (Fig 2b).

Passive Avoidance Test

There was no significant difference in first day latency among the groups. The second day latency (retention latency) significantly differed between the groups [$F (5,48)=13,955$, $p<0.0001$ (Fig. 3). Scopolamine significantly shortened the second day latency compared to the saline group ($p<0.001$). On the other hand, 6 and 9 mg/kg doses of mirabegron significantly prolonged retention latency compared to the saline group ($p<0.05$ and $p<0.001$, respectively). Furthermore, cognitive performance impaired with scopolamine has been significantly improved with 9 mg/kg mirabegron ($p<0.001$).

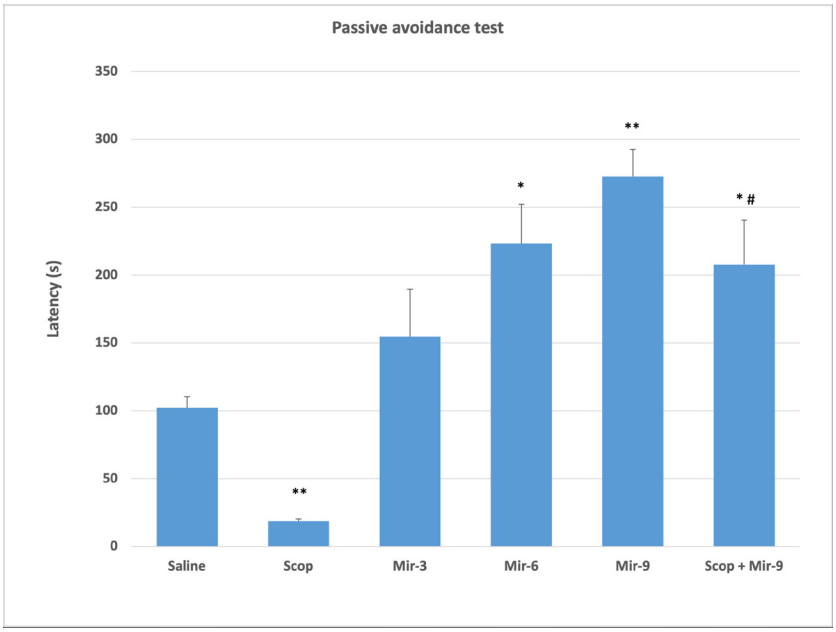

Figure 3. Effects of mirabegron on latency in passive avoidance test. Data were expressed as mean±SEM; (Saline (n=8); (Scop 0,6 mg/kg (n=8); Mir 3 mg/kg (n=8); Mir 6 mg/kg (n=8); Mir 9 mg/kg (n=8); Scop 0,6 mg/kg + Mir 9 mg/kg (n=8). *: *p*<0.05; **: *p*<0.001 compared to Saline group, by ANOVA (Tukey test) #: *p*<0.001 compared to Scop group, by ANOVA (Tukey test).

Morris Water Maze Test

There was a significant difference between drug groups or their combination [Two- way ANOVA post-hoc Tukey test; (F (5,53)=29,500; p<0.0001; Fig 4] in the time spent in the target quadrant during the probe trial of the MWM test when mirabegron groups were evaluated. Mirabegron (3 mg/kg) had no effect on the time spent in the target quadrant in naïve mice but mirabegron (6 and 9 mg/kg) significantly increased the time spent in the target quadrant in naïve mice (p<0.001). Scopolamine (0.6 mg/kg) significantly decreased the time spent in the target quadrant (p<0.001) but mirabegron (6 and 9 mg/kg) significantly prolonged the time spent in the target quadrant in scopolamine-treated mice (p<0.01) (Fig. 4a).

There was a significant difference between drug groups or their combination [Two- way ANOVA post-hoc Tukey's test; F(5,53)=17,005; p<0.0001; Fig 4b] in the mean distance to the platform in the probe trial of the MWM test when mirabegron groups were evaluated. Mirabegron (3, 6 and 9 mg/kg) had no effect on the mean distance to the platform in naïve mice. Scopolamine significantly increased the mean distance to the platform (p<0.001). Mirabegron (9 mg/kg) significantly decreased the mean distance to the platform in scopolamine-treated mice (p<0.001) (Fig. 4b), which suggests that it exerted some beneficial effects on disturbed memory.

There was a significant difference between drug groups or their combination [Two- way ANOVA post-hoc Tukey's test; F(5,53)=12,412; p<0.0001] in the swimming speed when mirabegron groups were evaluated. Scopolamine significantly increased the swimming speed (p<0.001). Mirabegron (3, 6 and 9 mg/kg) had no effect on swimming speed in naïve mice. Mirabegron (9 mg/kg) significantly decreased the swimming speed in scopolamine-treated mice (p<0.001) (Fig. 4c).

Effects of drugs on locomotor activity in the open field test

It is well known that the effects of drugs on depression, anxiety, learning and memory can be also evoked by drugs which induce hyperactivity or hypoactivity (Maj et al. 1992). Thus, the influence of all the above treatments on the locomotor activity was concurrently

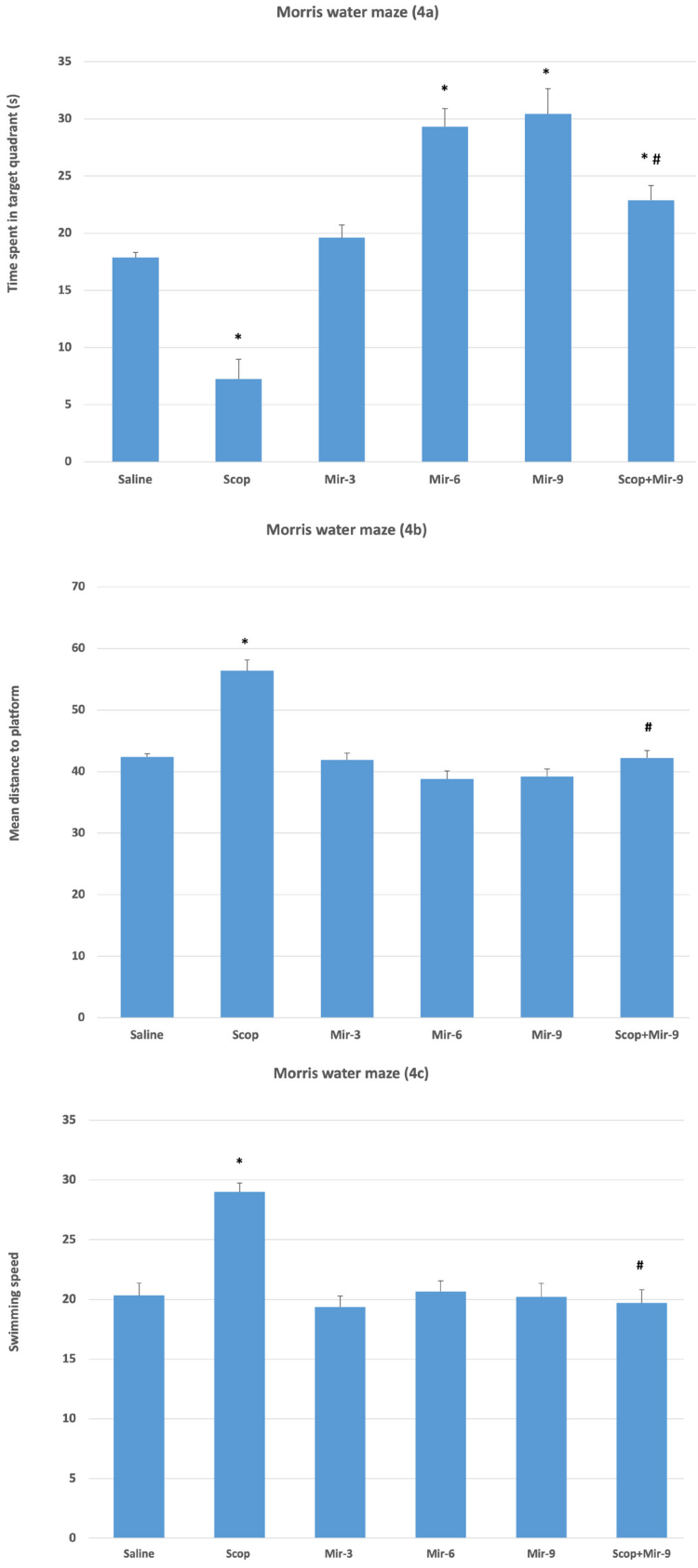

Figure 4. Effects of drugs on the time spent in target quadrant (4a), mean distance to platform (4b) and swimming speed (4c) in the probe trial of Morris water maze test. Data were expressed as mean±SEM; (Saline (n=9); (Scop 0,6 mg/kg (n=8); Mir 3 mg/kg (n=8); Mir 6 mg/kg (n=9); Mir 9 mg/kg (n=9); Scop 0,6 mg/kg + Mir 9 mg/kg (n=10). *: $p<0.001$ compared to Saline group, by ANOVA (Tukey test)#: $p<0.001$ compared to Scop group, by ANOVA (Tukey test).

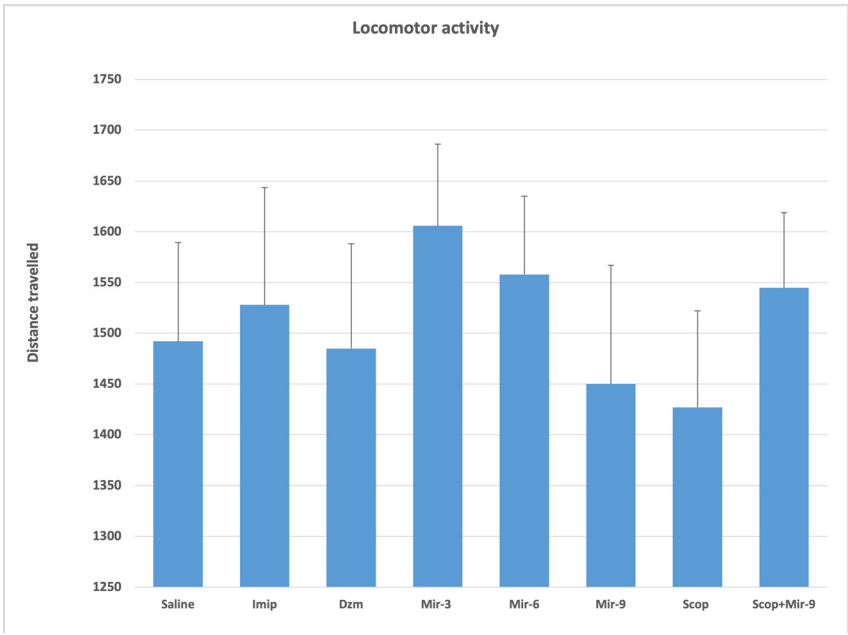

Figure 5. Effect of drugs on total distance traveled in locomotor activity test. Data were expressed as mean±SEM; (Saline (n=8); Imip 30 mg/kg (n=8); (Dzm 2 mg/kg (n=8); (Scop0,6 mg/kg (n=8); Mir 3 mg/kg (n=10); Mir 6 mg/kg (n=10); Mir 9 mg/kg (n=10); Scop 0,6 mg/kg + Mir 9 mg/kg (n=10).

evaluated. Neither mirabegron (3, 6 and 9 mg/kg) nor other drugs modified the total distance traveled [F(7,72)=0,3984; Fig. 5] in the open field test.

DISCUSSION

OAB is thought to contribute to development of psychiatric problems including anxiety and depression. It is claimed that OAB symptoms are prevalent among patients with psychological problems, and psychological problems are prevalent among patients with OAB (Nitti 2002). There are some studies investigating role of OAB in comorbid prevalence of anxiety and depression in patients (Melotti et al. 2018, Lai et al. 2016). Additionally, existence of the correlation between intensity of OAB symptoms with depression and anxiety or the relation with anxiety and depression levels and urgency incontinence and nocturia have been stated Melotti et al. 2017, 2018, Perry et al. 2006).

Although anxiety and depression are different mental disorders, their symptoms, causes, and treatments can often show similarities (Zbozinek et al. 2012). Anxiety disorders is one of the major mental illness groups and up to one third of people are affected by them during their lifetime (Zamorski & Ward 2000). While the exact underlying causes of anxiety disorders are unknown, some factors including psychological, environmental and genetic may play a role in the emergence of these. The role of abnormalities in the catecholaminergic and serotonergic neurotransmitter systems, decrease in serotonergic activity and dysregulation of the catecholaminergic systems have been noted previously in the pathogenesis of anxiety (Millan, 2003, Schloss & Williams 1998, Martin et al. 2009, Ressler & Nemeroff 2000).

Elevated plus-maze is one of the tests used to evaluate anxiety in animals. In the normal cases, the animals prefer to stay within the closed arms instead of open arms owing to feel more safe. Drugs with anxiolytic properties increase the time spent on the open arm. Results of our study revealed that diazepam (2 mg/kg) significantly increased the number of entries to the open arms with respect to saline group. Mirabegron did not have any effect on

the number of entries into the open arms when given 3 mg/kg dose. On the other hand, 6 and9 mg/kg doses of mirabegron significantly increased the number of entries into the open arms. In our previos study, we showed that amibegron (5 and 10 mg/kg) exerted anxiolytic-like effect, which was as effective as diazepam, in EPM test (Tanyeri et al. 2013a). Again, results of present study revealed that 6 and 9 mg/kg doses of mirabegron exerted anxiolytic effect, like as amibegron. These results suggest that beta 3-adrenergic receptor agonists can be usedin the treatment of anxiety other than OAB. Furthermore, patients with OAB who need to use anxiolytic drug can be treated with a single drug.

Several animal tests and models of depression are used for the determining of drug action. FST is the most widely used, fast, low cost and simple behavioural test for the screening of antidepressant drugs. FST is based on the measurement of an immobility time that is seen in rodents. The duration of immobility is measured after administration of drugs. Duration of immobility is significantly shorter in antidepressant drug given group compared to the control. Some experimental researches about the antidepressant activity of amibegron have been carried out to date. For example, antidepressant-like potential of amibegron in the chronic mild stress has been revealed in mice (Stemmelin et al. 2010). In one study, selective antidepressant-like effect of amibegron has been shown in Flinders Sensitive Line rat which is innately highly immobile in the forced swim test (Overstreet et al. 2008). In other study, it was demonstrated that amibegron counteracts stress-induced behavioral and neurochemical changes in rats subjected to acute or repeated restraint stress, applied prior to the FSTprocedure (Tamburella et al. 2010). Again, we investigate the antidepressant-like effect of amibegron and involvement of serotonin receptor subtypes in previous study. In this study using FST, 5 and 10 mg/kg doses of amibegron dose-dependently reduced the duration of immobility in mice (Tanyeri et al. 2013b). As for present study, imipramine and all doses of mirabegron significantly reduced duration of immobility compared to saline group. Our results are in agreement with the above-mentioned studies about the antidepressant-like profile of amibegron. Again, present and previous studies confirm that selective beta 3- adrenergic receptor agonists have antidepressant potential and hypothesis that beta 3- adrenergic receptor may be a therapeutic target for the treatment of stress-related disorders. There is not any difference between the used endications and effect mechanisms of mirabegron and amibegron.

It is known there is a relationship between serotonin synthesis and availability of its precursor tryptophan in the brain. Conversely, low tryptophan levels result in a decrease in brain serotonin synthesis which is one of the underlying reasons for the development of anxiety and depression (Poncet et al. 1993, Dursun et al. 2001). In a study about the effects of the amibegron on serotonergic and noradrenergic transmission in the rodent, it increased the synthesis of serotonin and tryptophan levels in several brain areas such as cortex, hippocampus, hypothalamus, striatum (Claustre et al. 2008). In other study, it has been suggested that activation of either β_2- or β_3-adrenergic receptors increases mouse brain tryptophan content (Lenard et al. 2003). In another study, it was shown that selective beta 3- adrenergic receptor antagonist SR59230A completely reversed the antidepressant-like activity of amibegron (Consoli et al. 2007). The above-mentioned studies revealed that beta 3-adrenergic receptor has an important role in the modulation of serotonergic

transmission in the brain (Stemmelin et al. 2008) Based on previous results, we claimed that beta 3-adrenergic receptor agonists have antidepressant and anxiolytic potentials and their activities, at least in part, may be related to modulation of serotonergic transmission.

It is a known fact, some compounds altering motor activity may lead to false positive or negative effects in behavioral tests. For example, psychostimulants which increase the general activity may cause false positive results in FST (Kedzierska & Wach 2016). For this reason, in the peresent study, we used the locomotor activity test to determine the impact of the investigated compound on locomotion. Neither mirabegron (3, 6 and 9 mg/kg) nor other drugs affected locomotor activity of mice in the open field test.

The passive avoidance (in other words, inhibitory avoidance) test is useful for the evaluation of cognitive performance (learning) and is based on the natural tendency of rodents. Rodents inherently tend to be in the dark environment. The animals avoid moving from the illuminated to the dark compartment of apparatus as they learn that they will be exposed to electric shocks in the dark section. There is a positive correlation between cognitive performance and the latency to moving from the illuminated compartment, the better the memory performance the longer the the latency. The Morris water maze is one of the most widely used behavioral test to examine the effects of drugs on spatial memory which is related to hippocampus and long-term potentiation (Vorhees & Williams 2006). In this test, animals are expected to solve the maze needed to escape from water. Some experimental models related to impairing cognitive functions have been developed. These models are widely used to reveal the effects of drugs that have therapeutic potential to treat cognitive disorders. Scopolamine or dizocilpine are frequently been used in cognition models to induce impairment and identify the potential of test compounds to reverse these impairments. In the present study, we preferred scopolamine to impair cognitive functions.

The prolongation of latency time in passive avoidance test is a sign of stronger learning performance. As in previous studies, scopolamine has caused a decrease in latency time in passive avoidance test; in other words, it has impaired cognitive functions. However, 6 and 9 mg/kg doses of mirabegron significantly prolonged the latency time with respect to saline group. Furthermore, cognitive performance impaired with scopolamine has been significantly improved with 9 mg/kg mirabegron. As a result, mirabegron not only recovered cognitive functions impaired by scopolamine, but also caused improvement in animals with cognitive functions were intact.

In the Morris water maze test, in a circular pool, animals must escape from the water to a small platform hidden just below the water surface. Twenty-four h after the last acquisition day, a probe trial is given to assess the spatial memory retention of the location of the hidden platform during this trial; the platform is removed from the maze. Some parameters such as the time spent in the target quadrant, the mean distance to the platform, and the swim speed are measured. It has been shown in previous studies that NMDA receptor antagonists MK-801 and phencyclidine impair reference memory in the MWM test (Tanyeri et al. 2015, Zain et al. 2018). Again, scopolamine is also impaire learning and reference memory in the MWM test (Nigam et al. 2019). In the present study, scopolamine decreased the time spent in the target quadrant, increased the mean distance traveled to the platform during the probe trial, and increased the swimming speed in MWM test. On the other hand, 6 and 9 mg/kg mirabegron increased the

time spent in the target quadrant in naive animal groups. Again, 9 mg/kg mirabegron reversed scopolamine-induced decrease in time spent in the target quadrant. All doses of mirabegron had no effect on mean distance traveled to the platform and swimming speed in naive mice during the probe trial. On the other hand, 9 mg/kg mirabegron significantly reversed scopolamine-induced increase in mean distance traveled to the platform and swimming speed. Results of mentioned above suggested that mirabegron has improved learning and memory in naive animals and impairments in learning and memory by scopolamine has been reversed with 9 mg/kg mirabegron.

Critical role of cholinergic system in learning and memory, dysfunction in central cholinergic system in age-related cognitive impairment or senile dementia are widely known fact. Additionally, disturbing effect of muscarinic cholinergic receptor antagonist scopolamine on learning and memory functions has also been shown in experimental studies (Nigam et al. 2019). In a recent study, the role of beta 3-adrenergic receptor in the process of acquisition of declarative memory has been shown (Souza-Braga et al. 2018). Again, it has been suggested that this action of beta 3-adrenergic receptor may be due to the facilitation of glucose absorption in the amygdala. Considering the results of our and previous studies, the following can be suggested: (1) recovery of scopolamine-impaired learning and memory by mirabegron may be partly associated with the enhancement of cholinergic transmission. The enhancement of cholinergic transmission may be result of inhibition of acetylcholinesterase enzyme or increasing release of acetylcholine from presynaptic nerve terminals. (2) The fact that mirabegrone has improved learning and memory performance in animals also may be partly related to its facilitatory effect on glucose absorption in related neurons via beta 3-adrenergic receptors (Souza-Braga et al. 2018). As a result; Mirabegron might be clinically useful for the treatment of OAB in elderly patients that should use drugs against depression and anxiety, without disrupt learning and memory.

In conclusion, mirabegron has shown an antidepressant- and anxiolytic-like effects, improved the memory and learning of naive animals and reversed the memory and learning impaired with scopolamine. Patients with OAB who need antidepressant and anxiolytic treatment can be treated with a single drug instead of multiple medications. Again, some side effects that worsen symptoms of dementia in elderly patients related to antidepressants (with anticholinergic effect) and anticholinergics used in OAB will not be seen in mirabegron users. Further preclinical and clinical studies with mirabegron should be done to support all these hypothesis and these findings will open new horizons to develop drugs for OAB with depression and anxiety in the future. Additionally, these results revealed that beta 3-adrenergic receptor may be an alternative target for novel antidepressant or anti-dementia drug development.

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