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Duloxetine reverses the symptoms of overactive bladder co-existing with depression via the central pathways

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ABSTRACT

Though the association between overactive bladder (OAB) and depression was noticed years ago, the pharmaceutical market does not offer one universal drug that would cure both conditions at the same time. The main goal of our present experiments was to determine whether a 14-day administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), or duloxetine (1 mg/kg/day) would reverse detrusor overactivity and depression-like signs in female Wistar rats subjected to corticosterone treatment. Surgical procedures, cystometric studies, biochemical analyses, and the forced swim test were performed according to published literature. After 14 days of exposure to corticosterone (20 mg/kg/day, subcutaneously), the tested animals presented symptoms of depression, detrusor overactivity, inflammation, and disturbances in neurotrophic factors. The obtained results demonstrated that solifenacin and mirabegron act mainly via peripheral pathways in OAB, whereas the central pathways are responsible for the effects of duloxetine. 72 h after discontinuation of duloxetine treatment, positive changes in the corticosterone-induced depression, detrusor overactivity, and inflammation were observed. Duloxetine seems to have a potential to become a new treatment option for patients with OAB co-existing with depression.

1. Introduction

The association between overactive bladder (OAB) and depression was noticed years ago. The systematic review by Vrijens et al. (2015) demonstrated that 26 out of 35 studies indicated the positive association between OAB and depression, while none of the analysed trials showed the negative one. On the one hand, significant deterioration of patient's quality of life caused by OAB symptoms generates stress and thus may lead to the development of mood disorders (Lai et al., 2016). On the other hand, depression, which is associated with stress, or taking antidepressant drugs may be a risk factor for new-onset OAB (Hirayama et al., 2012; Solmaz et al., 2017). Frequent co-existance of OAB and depression may also be due to the fact that several common biological pathways are implicated in the pathomechanism of these syndromes. Recent studies by Lai et al. (2016) revealed that 27.5% of adult patients (women and men) with OAB had depression, whereas in the clinical trial by Melotti et al. (2018), the percentage of women with OAB accompanied by depression was even higher – up to 60%. Subjects with depressive disorder present more severe incontinence, and their self-motivation to participate in the behavioural therapy and/or to take the prescribed drugs regularly is significantly lower (Lai et al., 2016). Globally, the number of patients concerned by this dual problem is considerable. About 400 million people report urinary urgency and frequency (which are the symptoms of so-called “dry” OAB), and a proportion of them additionally report urgency incontinence (a symptom of so-called “wet” OAB). It has been estimated that even 30–40% of people over 75 suffer from OAB, as the risk of this disease is higher with age (Irwin et al., 2006). According to the newest report of the World Health Organization (2017), the total number of people suffering from depression in 2015 exceeded 320 million.

The first-line treatment for OAB are antimuscarinic drugs, whereas depression is usually treated with medicinal products that modulate the monoaminergic (i.e., serotonergic, noradrenergic, or dopaminergic) neurotransmissions. So far, the pharmaceutical market is not able to

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offer one universal drug that would cure both conditions at the same time, but based on pre-clinical data, such a two-way treatment is possible. Imbalance in the serotonergic and noradrenergic neurotransmissions, disturbances in the limbic system, inflammation process as well as dysfunctions in signalling dependent on the corticotropin-releasing factor (CRF) or Rho kinase are engaged in the pathomechanism of both OAB and depression. It was shown that imipramine, a typical antidepressant drug could be useful in dry OAB. It reversed the changes in several cystometric parameters related to detrusor overactivity (DO) as well as it significantly diminished the increased levels of CRF in plasma, hippocampus, and amygdala in rats exposed to 13-cis-retinoic acid (Wrobel et al., 2017). Moreover, in the cyclophosphamide-induced model of OAB, imipramine (20 mg/kg, intraperitoneally) significantly reduced signs of urgency (Redaelli et al., 2015). In fact, this tricyclic antidepressant decreased bladder contractility, increased outlet resistance, and improved urine storage also in humans. A single night-time dose of imipramine (25–150 mg) taken by elderly people with detrusor instability alleviated their lower urinary tract symptoms (Castleden et al., 1981). Another tricyclic antidepressant, doxepin, prescribed at a dose of 50–75 mg reduced both night-time frequency and night-time episodes of incontinence (Lose et al., 1989). The outcomes of our previous experiments demonstrated that inhibition of the CRF1 receptors by SN003 (Wrobel et al., 2017; Wrobel et al., 2016), inhibition of Rho kinase by GSK 269962 (Wrobel et al., 2018a), and inhibition of myosin II by blebbistatin (Wrobel et al., 2018b) improved both cystometric parameters and depressive behaviour in an animal model of DO and depression.

In view of the above, the goal of our present experiments was to determine whether a 14-day administration of solifenacin, mirabegron, or duloxetine would reverse DO and depression-like signs in rats subjected to corticosterone treatment. DO co-exists with OAB: ca. 64% of patients suffering from OAB have DO, and 83% of patients presenting DO have symptoms of OAB (Abrams and Andersson, 2007). Solifenacin acts as a competitive antagonist of muscarinic receptors, and it is indicated as the first-line drug in the treatment of OAB. Solifenacin inhibits acetylcholine activity on autonomic nerve endings and thus, it decreases bladder motility, enhances bladder capacity as well as it reduces contractions and urgency of urination (Luo et al., 2012). Mirabegron is a selective agonist of β3-adrenergic receptors, and it is usually used as the second-line therapy in patients with OAB. Stimulation of the β3-adrenoceptors in the bladder leads to bladder relaxation, increased urine storage, reduced bladder contraction, and diminished unwanted urinations (Deeks, 2018). As for duloxetine, it belongs to the serotonin norepinephrine reuptake inhibitors (SNRIs), and though primarily approved for treatment of depression and generalized anxiety disorder, this drug is also prescribed for stress urinary incontinence. Recently, the SNRIs have emerged as a promising alternative in the treatment of OAB (Di Rezze et al., 2012). Wang et al. (2015) reported the first case of beneficial effects of duloxetine therapy in a female patient with OAB co-existing with depression.

In the preliminary experiments carried out in our lab, it was demonstrated that a single intravenous dose of solifenacin, mirabegron, or duloxetine improved DO symptoms, but only the latter was able to reverse the depression-like behaviour in rats subjected to the 13-cis-retinoic acid treatment (Wrobel et al., 2017; Wróbel et al., 2018). Since a delayed onset of activity is specific to most of the antidepressant drugs, it seemed reasonable to confirm the results from acute experiments in a prolonged study. Moreover, we wanted to verify whether the results observed in the cystometric studies were due to the peripheral or central activity of the tested agents. Additionally, we decided to check the effects of the tested drugs on the hippocampus, prefrontal cortex, Barrington's nucleus, urinary bladder, and urine levels of Interleukin 1β (Il-1β), CRF, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and tumor necrosis factor α (TNF-α). All of these biomarkers are involved in nerve growth or inflammation and they are related to both DO and depression. Since OAB as well as depression are more frequently diagnosed in women than in men (Melotti et al., 2018; Irwin et al., 2006; World Health Organization, 2017), the experiments were carried out in female rats.

2. Materials and methods

This study was carried out in accordance with binding Polish and European law related to the experimental studies on animal models. The protocol was approved by the Local Ethics Committee in Lublin, Poland (licence no. 21/2017).

2.1. Animals

96 female Wistar rats were used in the experiments. Their initial weight was 200–225 g. The tested rats were kept in metabolic cages in environmentally controlled rooms (temperature of 22–23 °C, natural light/dark cycle, relative humidity ca. 45–55%) with ad libitum access to water and food. The animals were experimentally naïve, tested only once, and they were assigned to one of the following treatment groups that received:

1. Vehicle for 14 days plus vehicle for 14 days (the control group)
2. Corticosterone (20 mg/kg/day) for 14 days plus vehicle for 14 days
3. Vehicle for 14 days plus solifenacin (0.03 mg/kg/day) for 14 days
4. Corticosterone (20 mg/kg/day) for 14 days plus solifenacin (0.03 mg/kg/day) for 14 days
5. Vehicle for 14 days plus mirabegron (1 mg/kg/day) for 14 days
6. Corticosterone (20 mg/kg/day) for 14 days plus mirabegron (1 mg/kg/day) for 14 days
7. Vehicle for 14 days plus duloxetine (1 mg/kg/day) for 14 days
8. Corticosterone (20 mg/kg/day) for 14 days plus duloxetine (1 mg/kg/day) for 14 days

Each experimental group consisted of 10–12 animals. The treatment schedule was presented in Fig. 1.

2.2. Drugs

For the first 14 days of the experiments the animals received subcutaneous (s.c.) injections of corticosterone (Tocris) and then, they were given solifenacin (Astellas Pharma, Tokyo, Japan), mirabegron (Astellas Pharma, Tokyo, Japan), or duloxetine (Eli Lilly, Indianapolis, IN, USA) for 14 days into the right femoral vein. Solifenacin and mirabegron were dissolved in 1% DMSO solution, whereas duloxetine was dissolved in distilled water. The control group received vehicle, i.e., a mixture of physiological saline and 1% DMSO solution, at a ratio of 1:1, resulting in a final concentration of 0.5% DMSO. The volume of all administered solutions was 1 ml/kg body weight. The pretreatment schedules as well as the applied doses were chosen on the basis of the available literature and the results of previous studies performed in our lab (Wrobel et al., 2017; Wróbel et al., 2018).

2.3. Surgical procedures

The surgical procedures were carried out in the same way as had been previously described (Wróbel and Rechberger, 2017b). The abdominal wall was opened with a vertical midline incision of approximately 10 mm. A double lumen catheter was inserted through the apex of the bladder dome and fixed with a 6–0 suture. In the same session the carotid artery was cannulated. To prevent an infection of the urinary tract, 100 mg of cefazolin sodium hydrate (Biofazolin, Sandoz) was given s.c. All the surgical procedures were performed under anaesthesia with an i.p. injection of ketamine hydrochloride (75 mg/kg; Ketanest, Pfizer) and xylazine (15 mg/kg; Sedazin, Biowet). Rats were laid down supine on a warm mattress (37 °C). A sufficient depth of anaesthesia was measured by lack of spontaneous movement and lack of

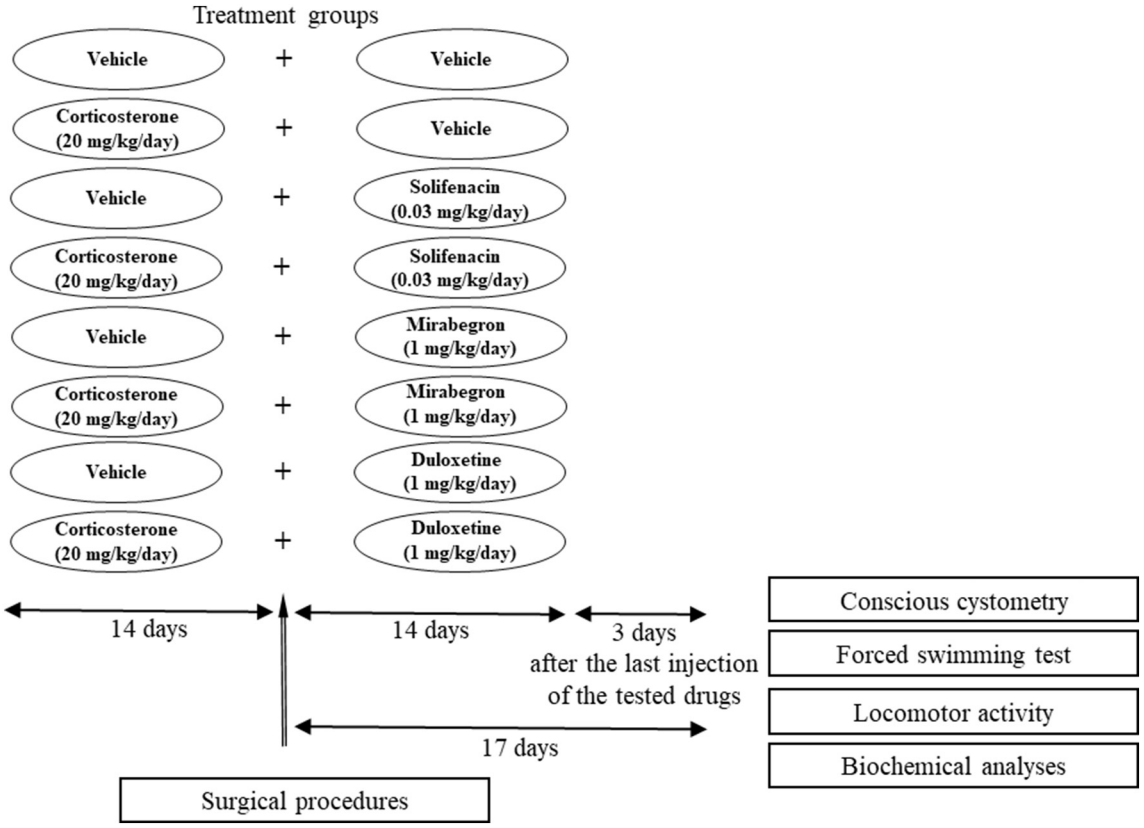

Fig. 1. Treatment schedule.

withdrawal response to noxious toe pinch.

2.4. Conscious cystometry

Cystometric measurements were carried out 17 days after the surgical procedures (i.e. 3 days after the last injection of the tested drugs) in the same way as had been previously described (Wrobel et al., 2016). The bladder catheter was connected via a three-way stopcock to a pressure transducer (FT03; Grass Instruments) and to a microinjection pump (CMA 100; Microject, Solna, Sweden). Cystometry was performed by slowly filling the bladder with physiological saline at a constant rate 0.05 ml/min to elicit repetitive voiding. Micturition volumes were measured by means of a fluid collector attached to a force displacement transducer (FT03C; Grass Instruments). The measurements in each animal represent the average of five bladder micturition cycles after obtaining repetitive voiding. The following cystometric parameters were recorded: amplitude of nonvoiding contractions (ANVC; cm H_2O), bladder compliance (BC; ml/cm H_2O), bladder contraction duration (BCD; s), detrusor overactive index (DOI; cm H_2O/ml), frequency of nonvoiding contractions (FNVC; times/filling phase), intercontraction interval (ICI; s), micturition voiding pressure (MVP; cm H_2O), postvoid residual (PVR; ml), and relaxation time (RT; s). The clinical meaning of these parameters has been described previously (Wrobel et al., 2016).

2.5. Behavioural studies

The behavioural studies were carried out 72 h after the last injection of solifenacin, mirabegron, or duloxetine.

2.5.1. Forced swim test

The FST was carried out in accordance with the method elaborated by Porsolt et al. (1977). At first, the pre-test was performed. Each animal was put individually into a dedicated glass cylinder (diameter 25 cm, height 65 cm) filled with water (temperature of 23–25 °C) and it stayed there for 15 min. After 24 h, the standard test was carried out. It was performed under identical conditions as the pre-test but it lasted for 5 min. An animal was judged immobile when it remained floating passively, performing only slow movements to keep its head above the water.

2.5.2. Locomotor activity

The spontaneous locomotor activity was measured in an Optical Animal Activity Monitoring System (Digiscan apparatus; Omnitech Electronics, Columbus, OH, USA). The activity score was recorded as an interruption of the infrared light beam by a tested animal. 1-h horizontal activity was assessed. Before the standard analysis, a 15-min habituation period was introduced.

2.6. Biochemical analyses

After the cystometric and behavioural studies, the animals were killed by decapitation and their brains and urinary bladder tissue were collected. The following parameters were measured in the hippocampus, prefrontal cortex, Barrington's nucleus, urinary bladder, and urine of the tested rats: Interleukin 1-β (ELISA Kit for IL1b, Cloud-Clone, USA), brain-derived neurotrophic factor (BDNF Emax®ImmunoAssay System PROMEGA, USA), corticotropin releasing factor (Mouse/Rat CRF-HS ELISA Kit, Alpco, Salem, NH, USA), nerve growth factor (Rat NGF ELISA Kit, LifeSpan BioSciences, USA), and tumor necrosis factor α (ELISA Kit for TNF Alpha, LifeSpan BioSciences, USA). Preparation of the samples as well as the measurements were performed according to the manufacturers' instructions.

2.7. Statistical analysis

The statistical measurements were carried out using two-way

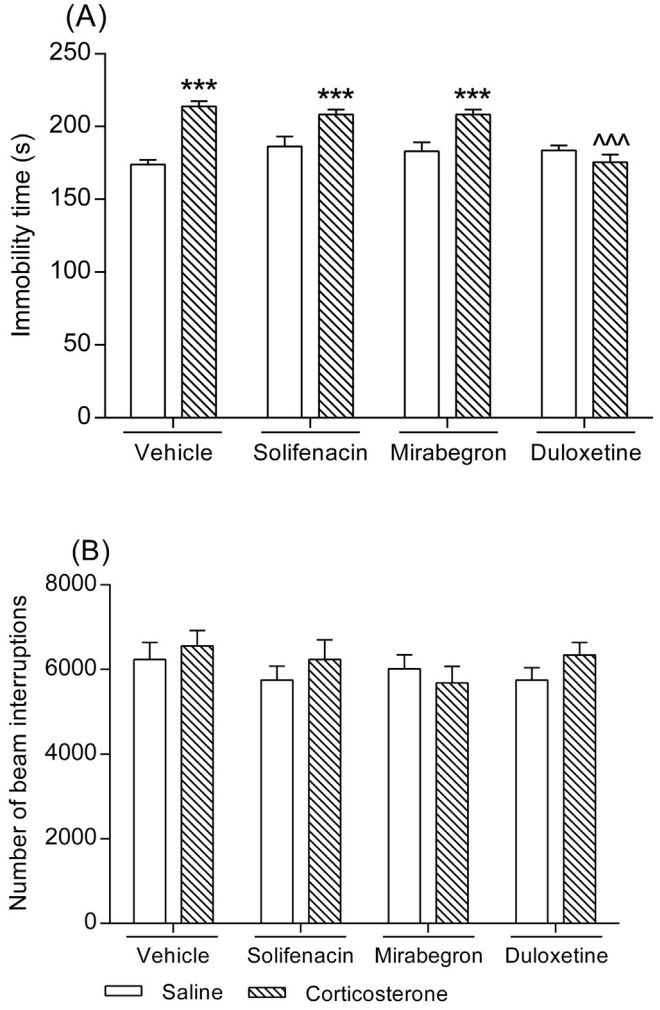

Fig. 2. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on the behaviour of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.) (A) in the forced swim test and (B) in the measurement of locomotor activity. The values represent the mean + SEM (n = 12 rats per group). ***$p < 0.001$ versus vehicle-treated group, ^^^$p < 0.001$ versus corticosterone-treated group (Bonferroni's post hoc test).

analysis of variance (ANOVA) followed by Bonferroni's post hoc test. The obtained results were presented as the means ± standard error of the mean (SEM). A difference between the tested groups was considered as statistically significant when $p < 0.05$.

3. Results

3.1. Forced swim test

As was presented in Fig. 2A, after the 14-day administration of corticosterone (20 mg/kg/day) the tested rats were significantly more immobile than the vehicle-treated group. The depressogenic-like effect was reversed only by the 14-day therapy with duloxetine (1 mg/kg/day). Neither solifenacin (0.03 mg/kg/day) nor mirabegron (1 mg/kg/day) reversed the corticosterone-induced effects. Two-way ANOVA demonstrated a significant corticosterone-duloxetine interaction [$F(1,44) = 36.52$; $p < 0.0001$] with a significant effect of corticosterone [$F(1,44) = 16.12$; $p = 0.0002$] and a significant effect of duloxetine [$F(1,44) = 12.94$; $p = 0.0008$]. The interactions between corticosterone and solifenacin or mirabegron were not considered as significant [$F(1,42) = 4.00$; $p = 0.0521$ for corticosterone-solifenacin; F

Table 1
Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on the cystometric parameters in conscious rats subjected to corticosterone therapy.

	Amplitude of nonvoiding contractions cm H_2O	Bladder compliance ml/cm H_2O	Bladder contraction duration	Detrusor overactive index cm H_2O/ml	Frequency of nonvoiding contractions times/filling phase	Intercontraction interval s	Micturition voiding pressure cm H_2O	Postvoid residual ml	Relaxation time s
Saline (14 days) + vehicle (14 days)	2.357 ± 0.1299	0.1960 ± 0.0024	30.17 ± 1.762	88.58 ± 8.239	0.5400 ± 0.0421	875.3 ± 24.85	37.39 ± 4.005	0.0623 ± 0.0034	23.72 ± 1.058
CORT (14 days) + vehicle (14 days)	4.730 ± 0.2742***	0.1528 ± 0.0055***	32.25 ± 2.178	355.2 ± 22.34***	5.770 ± 0.5762***	654.9 ± 35.69***	32.05 ± 2.265	0.0497 ± 0.0044	22.67 ± 0.9386
Saline (14 days) + solifenacin (14 days)	2.125 ± 0.1911	0.2033 ± 0.0062	30.92 ± 2.244	93.92 ± 3.241	0.6500 ± 0.0563	900.7 ± 13.35	30.70 ± 1.942	0.0774 ± 0.0077	26.71 ± 0.9320
CORT (14 days) + solifenacin (14 days)	4.579 ± 0.3792***	0.1648 ± 0.0053***	29.00 ± 1.624	406.5 ± 25.79***	4.327 ± 0.4375***^	716.0 ± 64.47*	34.68 ± 3.871	0.0711 ± 0.0075	22.70 ± 1.080
Saline (14 days) + mirabegron (14 days)	2.545 ± 0.1389	0.1832 ± 0.0027	27.72 ± 1.109	134.8 ± 11.12	1.301 ± 0.1521	895.9 ± 45.45	30.83 ± 4.145	0.0576 ± 0.0050	24.61 ± 1.199
CORT (14 days) + mirabegron (14 days)	3.758 ± 0.2982***^^	0.1675 ± 0.0038***^	30.83 ± 1.898	289.1 ± 26.53***^	4.461 ± 0.2906***^	545.8 ± 36.87***	37.42 ± 2.175	0.0629 ± 0.0076	26.42 ± 1.143
Saline (14 days) + duloxetine (14 days)	2.128 ± 0.03896	0.1929 ± 0.0047	28.92 ± 1.018	111.1 ± 18.19	0.9858 ± 0.1515	962.1 ± 28.43	32.31 ± 2.118	0.0629 ± 0.0056	26.99 ± 1.173
CORT (14 days) + duloxetine (14 days)	2.868 ± 0.1985^^	0.2118 ± 0.0063^^	29.58 ± 1.495	107.4 ± 9.361^^	1.298 ± 0.1767^^	982.0 ± 36.49^^	36.25 ± 2.781	0.1270 ± 0.0583	24.90 ± 1.105

Corticosterone (CORT, 20 mg/kg/day) was given subcutaneously for 14 days and solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), or duloxetine (1 mg/kg/day) were administered intravenously for 14-days. The values represent the mean + SEM (n = 10–12 mice per group). The obtained data were assessed by the two-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test.
*$p < 0.05$, ***$p < 0.001$ versus saline, ^$p < 0.05$, ^^$p < 0.01$, ^^^$p < 0.001$ versus CORT.

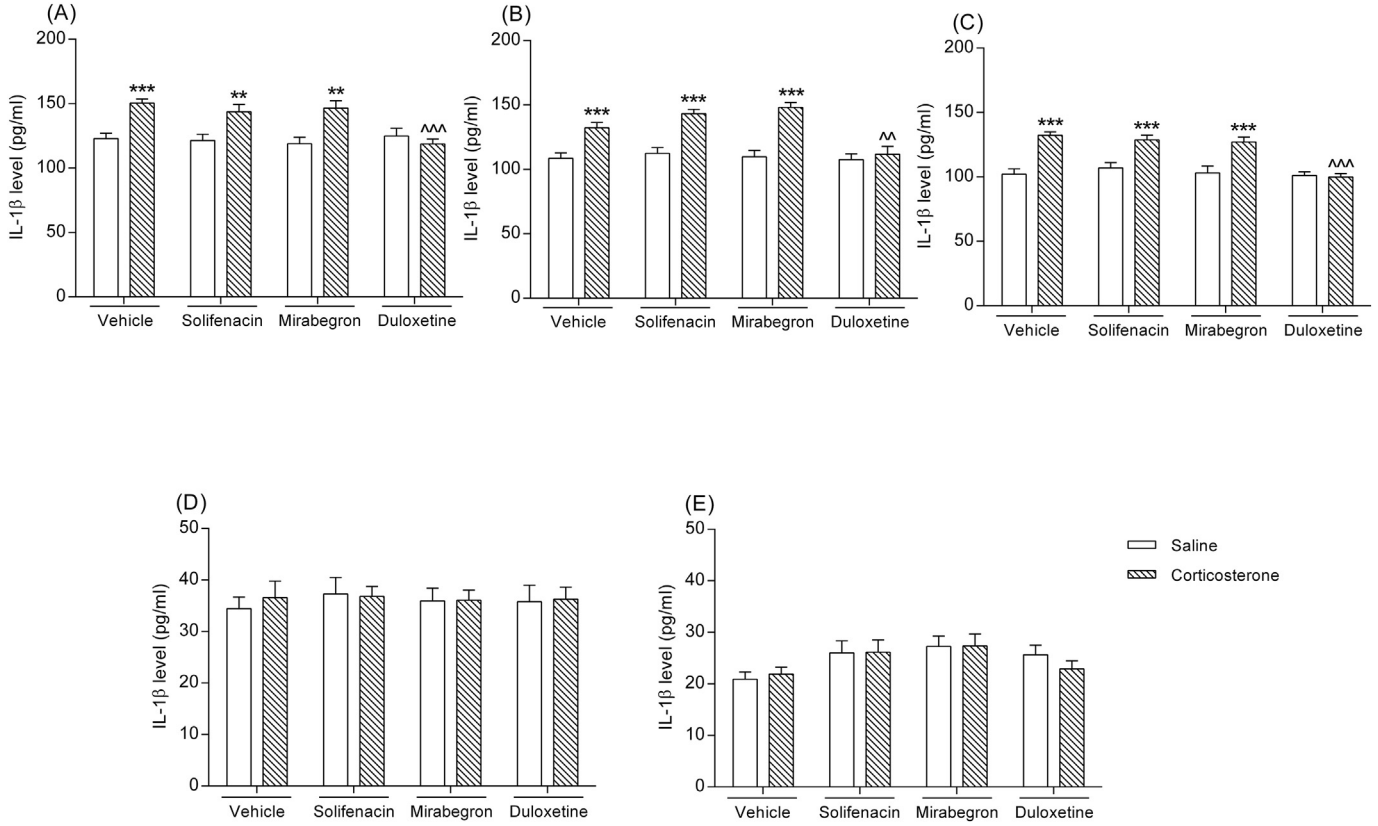

Fig. 3. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on Interleukin 1β (IL-1β) levels in the (A) hippocampus, (B) prefrontal cortex, (C) Barrington's nucleus, (D) urinary bladder and (E) urine of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.). The values represent the mean + SEM (n = 11–12 rats per group). $^{**}p < 0.01$, $^{***}p < 0.001$ versus vehicle-treated group, ^^p < 0.01, ^^^p < 0.001 versus corticosterone-treated group (Bonferroni's post hoc test).

(1,44) = 3.01; p = 0.0900 for corticosterone-mirabegron]. The swimming pattern of rats that received only solifenacin, mirabegron, or duloxetine for 14 days was comparable to the one observed for the control group.

3.2. Locomotor activity

None of the tested drugs given alone or in respective combinations influenced the locomotor activity of animals (Fig. 2B).

3.3. Cystometric study

The 14-day pretreatment with corticosterone (20 mg/kg/day) resulted in considerable changes in several cystometric parameters. A significant increase in ANVC, DOI, and FNVC, accompanied by a significant decrease in BC and ICI were recorded. The values of BCD, MVP, PVR, and RT were not significantly influenced by either of the administered agents. As was summarised in Table 1, the 14-day treatment with solifenacin (0.03 mg/kg/day) did not manage to reverse the corticosterone-induced cystometric changes specific to DO. The 2-week administration of mirabegron (1 mg/kg/day) partially reduced the elevated ANVC, DOI, and FNVC levels, and moderately increased the diminished BC values. As for duloxetine, when given for 14 days at a dose of 1 mg/kg/day, it significantly reversed all of the noxious effects induced by the exposure to corticosterone. The positive effects of duloxetine therapy were confirmed by two-way ANOVA, which revealed a significant pretreatment-treatment interaction resulting in reduction in ANVC [F(1,44) = 20.06; $p < 0.0001$], DOI [F(1,44) = 74.11; $p < 0.0001$], and FNVC [F(1,43) = 69.46; p < 0.0001], and a significant corticosterone-duloxetine interaction resulting in a raise of BC [F(1,44) = 39.39; p < 0.0001] and ICI [F(1,43) = 14.15; p = 0.0005].

3.4. Biochemical study

Neither solifenacin (0.03 mg/kg/day) nor mirabegron (1 mg/kg/day) or duloxetine (1 mg/kg/day) when given for 14 days to the vehicle-treated animals affected levels of IL1-β, CRF, BDNF, NGF, and TNF-α.

3.4.1. Interleukin 1β levels

As suspected, the 14-day corticosterone therapy (20 mg/kg/day) significantly increased levels of IL1-β in the hippocampus (by ca. 22% vs. control group), prefrontal cortex (by ca. 22%), and the Barrington's nucleus (by ca. 29%). It did not change IL1-β values in the urinary bladder and urine (Fig. 3). Neither solifenacin (0.03 mg/kg/day) nor mirabegron (1 mg/kg/day) when given for 14 days reversed the effects of corticosterone. However, the duloxetine treatment (1 mg/kg/day given for 14 days) normalized concentrations of IL1-β in the tested brain areas of animals exposed to corticosterone. Two-way ANOVA revealed significant corticosterone-duloxetine interactions for the analysis of hippocampus [F(1,44) = 14.50; p = 0.0004], prefrontal cortex [F(1,44) = 4.07; p = 0.0497], and the Barrington's nucleus [F(1,44) = 24.46; $p < 0.0001$].

3.4.2. Corticotropin releasing factor levels

Rats given the corticosterone treatment (20 mg/kg/day) for 14 days had significantly elevated CRF values in all the tested samples, i.e. in the hippocampus (by 246% vs. control group), prefrontal cortex (by ca. 315%), Barrington's nucleus (by ca. 319%), urinary bladder (by ca. 28%), and urine (by ca. 17%). The 14-day administration of mirabegron (1 mg/kg/day) did not significantly influence the corticosterone-induced changes in CRF levels. The 2-week therapy with solifenacin (0.03 mg/kg/day) reversed the noxious effects of corticosterone in the

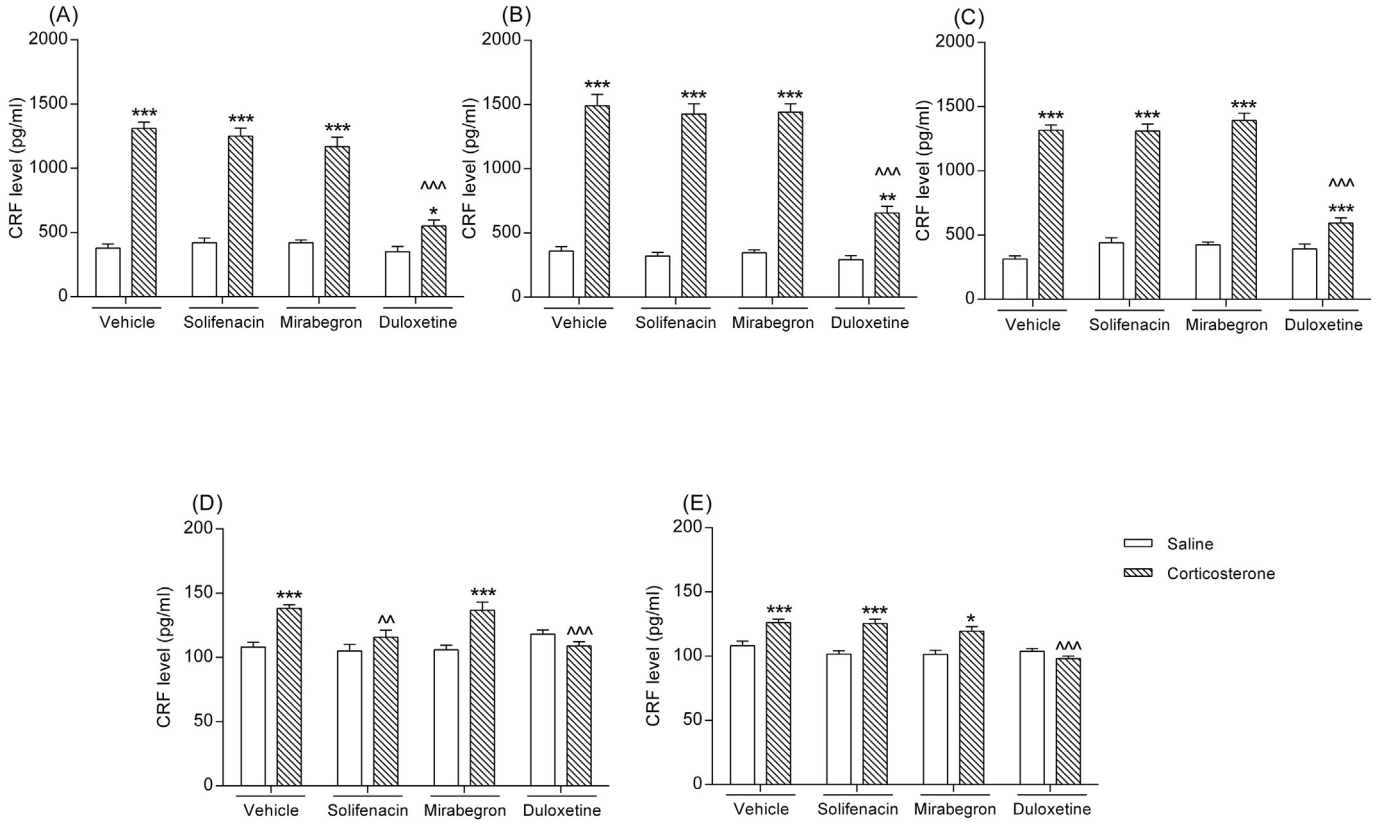

Fig. 4. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on levels of corticotrophin release factor (CRF) in the (A) hippocampus, (B) prefrontal cortex, (C) Barrington's nucleus, (D) urinary bladder and (E) urine of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.). The values represent the mean + SEM (n = 10–12 rats per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus vehicle-treated group, ^^p < 0.01, ^^^p < 0.001 versus corticosterone-treated group (Bonferroni's post hoc test).

urinary bladder. Two-way ANOVA demonstrated a significant corticosterone-solifenacin interaction: F(1,42) = 5.11, p = 0.0290. As for duloxetine given for 14 days at a dose of 1 mg/kg/day, it partially restored the elevated levels of CRF in the hippocampus (two-way ANOVA detected a significant pretreatment-treatment interaction: F(1,43) = 77.11; p < 0.0001), prefrontal cortex (a significant pretreatment-treatment interaction: F(1,44) = 46.62; p < 0.0001) and in the Barrington's nucleus (a significant pretreatment-treatment interaction: F(1,44) = 116.19; p < 0.0001). Moreover, it totally restored the elevated levels of CRF in the urinary bladder (a significant pretreatment-treatment interaction: F(1,44) = 35.53; p < 0.0001) and urine (a significant pretreatment-treatment interaction: F(1,44) = 20.01; p < 0.0001). The results were presented in Fig. 4.

3.4.3. Brain-derived neurotrophic factor levels

Fig. 5 illustrates changes in BDNF levels after the introduced treatment in rats. Animals subjected to the 14-day administration of corticosterone at a dose of 20 mg/kg/day presented much lower BDNF values when compared to the vehicle-treated group, except for the urine samples. The BDNF levels were diminished in the hippocampus (by ca. 11%), in the prefrontal cortex (by ca. 16%), in the Barrington's nucleus (by ca. 12%), in the urinary bladder (by ca. 16%). In urine, they were increased by ca. 63%. Both solifenacin (0.03 mg/kg/day) and mirabegron (1 mg/kg/day) therapy given for 14 days reversed the corticosterone-induced changes in the bladder and urine values of BDNF. In the case of mirabegron, two-way ANOVA indicated a significant pretreatment-treatment interaction for the analysis of the urinary bladder [F(1,44) = 5.11; p = 0.0288] and urine [F(1,43) = 10.30; p = 0.0025]. However, in the case of solifenacin, two-way ANOVA indicated a significant pretreatment-treatment interaction only for the analysis of urine [F(1,41) = 4.59; p = 0.0382]; the interaction for the analysis of the urinary bladder did not reach the significance level [F(1,44) = 2.26; p = 0.1399]. Duloxetine given at a dose of 1 mg/kg/day for 2 weeks restored concentrations of BDNF in all tested samples. Two-way ANOVA detected significant pretreatment-treatment interactions: F(1,43) = 25.95; p < 0.0001 for the analysis of the hippocampus, F(1,42) = 4.44; p = 0.0410 for the analysis of the prefrontal cortex, F(1,43) = 5.44; p = 0.0244 for the analysis of the Barrington's nucleus, F(1,44) = 8.89; p = 0.0047 for the analysis of the urinary bladder, and F(1,43) = 29.43; p < 0.0001 for the analysis of urine.

3.4.4. Nerve growth factor levels

Subcutaneous injections of corticosterone (20 mg/kg/day) for 14 days resulted in a significant decrease of NGF levels in the tested brain areas (by ca. 15% in the hippocampus, 19% in the prefrontal cortex, and 18% in the Barrington's nucleus vs. control group) as well as in the urinary bladder (by ca. 31%). On the other hand, more NGF was secreted in urine (by ca. 64%). The 14-day administration of solifenacin at a dose of 0.03 mg/kg/day normalized NGF levels in the hippocampus, urinary bladder, and urine. According to two-way ANOVA, a significant pretreatment-treatment interaction took place in the case of the hippocampus [F(1,43) = 5.59; p = 0.0226] and urine [F(1,44) = 6.77; p = 0.0126], but it did not reach the significance level in the case of the urinary bladder [F(1,41) = 1.51; p = 0.2255]. Mirabegron therapy (1 mg/kg/day for 14 days) managed to revert the changed NGF values to the control ones in the hippocampus, prefrontal cortex, urinary bladder, and urine. Statistical analysis demonstrated the following results regarding the corticosterone-mirabegron interaction: F(1,44) = 7.34; p = 0.0096 for the analysis of the hippocampus, F(1,56) = 14.96; p = 0.0003 for urinary bladder, F(1,43) = 4.35; p = 0.0430 for the analysis of the prefrontal cortex, F(1,42) = 4.99;

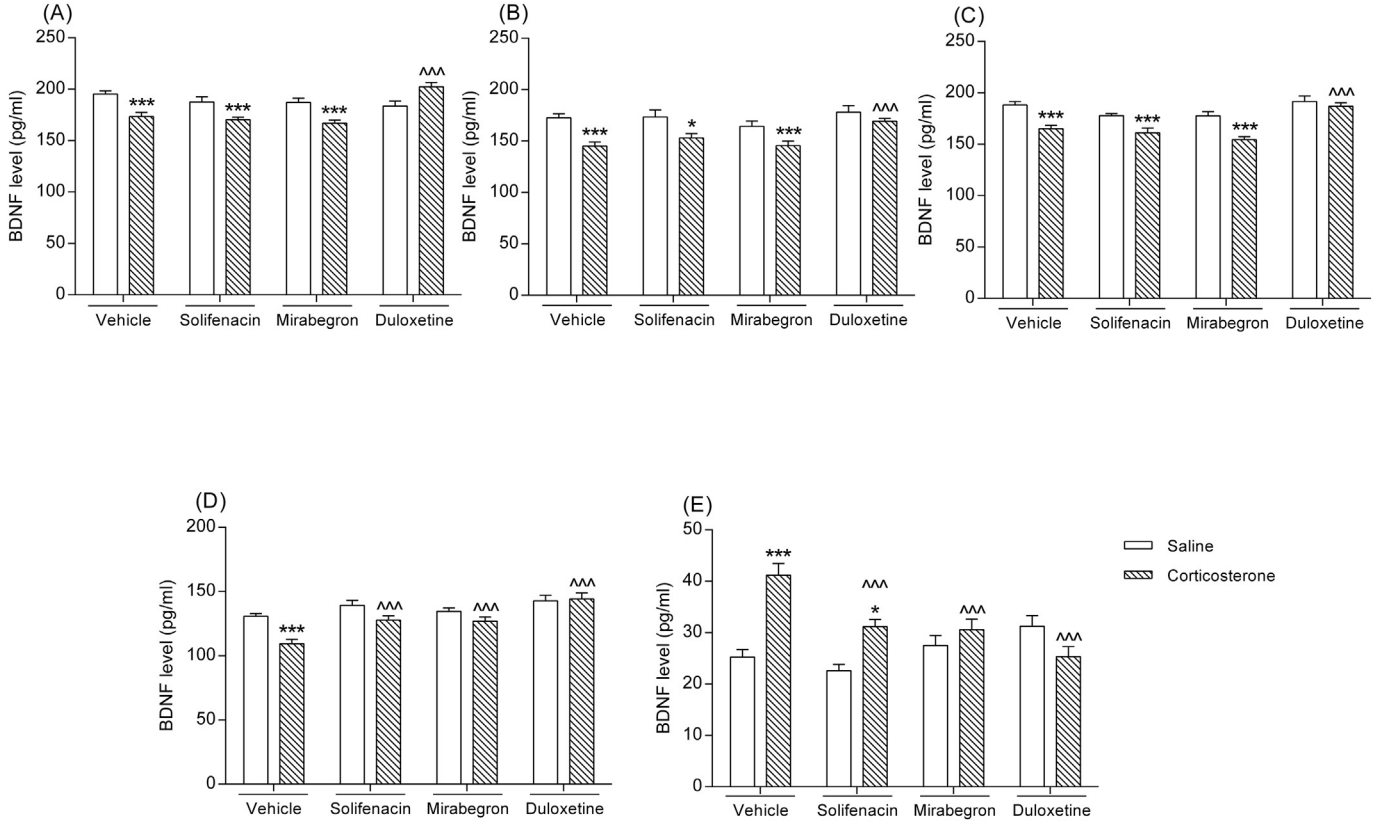

Fig. 5. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on levels of brain-derived neurotrophic factor (BDNF) in the (A) hippocampus, (B) prefrontal cortex, (C) Barrington's nucleus, (D) urinary bladder and (E) urine of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.). The values represent the mean + SEM (n = 10–12 rats per group). *p < 0.05, ***p < 0.001 versus vehicle-treated group, ^^^p < 0.001 versus corticosterone-treated group (Bonferroni's post hoc test).

$p = 0.0309$ for the analysis of the urinary bladder, and $F(1,44) = 12.50$; $p = 0.0010$ for the analysis of urine. As for the duloxetine treatment (1 mg/kg/day for 14 consecutive days), it reversed all the corticosterone-induced changes in NGF levels. A significant corticosterone-duloxetine interactions were detected in all respective statistical analyses: $F(1,44) = 31.10$; $p < 0.0001$ in the case of the hippocampus, $F(1,44) = 28.67$; $p < 0.0001$ in the case of the prefrontal cortex, $F(1,41) = 15.51$; $p = 0.0003$ in the case of the Barrington's nucleus, $F(1,43) = 17.70$; $p = 0.0001$ in the case of the urinary bladder, and $F(1,44) = 9.43$; $p = 0.0036$ in the case of urine (Fig. 6).

3.4.5. Tumor necrosis factor α levels

Rats exposed to the 14-day administration of corticosterone (20 mg/kg/day) presented considerably raised levels of TNF-α in the hippocampus (by ca. 25% vs. the vehicle-treated group), prefrontal cortex (by 23%), and the Barrington's nucleus (by ca. 32%). TNF-α levels in the urinary bladder and urine were not significantly changed (Fig. 7). Neither solifenacin (0.03 mg/kg/day) nor mirabegron (1 mg/kg/day) when given for 14 days normalized the TNF-α values in the tested brain areas. However, the 14-day duloxetine treatment (1 mg/kg/day) reversed all noxious changes in TNF-α levels induced by corticosterone exposure. Two-way ANOVA indicated significant pretreatment-treatment interactions: $F(1,42) = 38.15$; $p < 0.0001$ for the analysis of the hippocampus, $F(1,44) = 18.40$; $p < 0.0001$ for the analysis of the prefrontal cortex, $F(1,44) = 5.43$; $p = 0.0244$ for the analysis of the Barrington's nucleus.

4. Discussion

Based on the outcomes of our previous experiments, the corticosterone model of DO and depression applied in the present experiments is a reliable paradigm for the assessment whether a given agent has a potential to be used in OAB accompanied by depressive symptoms. This model significantly responded to both oxybutynin chloride (a standard antimuscarinic drug) and conventional antidepressants, like imipramine and fluoxetine (Wrobel et al., 2016). As expected, after the 14-day exposure to corticosterone, the tested animals presented the depressive-like behaviour in the FST and the signs of DO easily assessed in the cystometric studies. Their ANVC, DOI, and FNVC values were significantly elevated, whereas the BC and ICI levels were decreased. Additionally, corticosterone-treated rats presented signs of inflammation and disturbances in neurotrophic factors, which are specific to both DO and depression. The biochemical tests confirmed elevated concentrations of the pro-inflammatory markers (IL-1β, TNF-α) in the brain tissue. Neuroinflammation and pro-inflammatory cytokines (including IL-1β and TNF-α) seem to be implicated in the pathomechanism of both conditions (Jeon and Kim, 2016; Hurst et al., 2007). The literature data (Hurst et al., 2007) indicated that patients with OAB may present elevated levels of serum or urinary inflammatory biomarkers, including TNF-α. Similarly IL-1β levels in cerebrospinal fluid (CSF), serum, or urine (Howren et al., 2009) as well as TNF-α values in serum (Schmidt et al., 2014) are frequently significantly higher in patients suffering from different types of depression in comparison to the non-depressed people. On the other hand, in patients with endotoxin- or vaccine-induced elevation of IL-1β and TNF-α, a transient intensification of depression symptoms has been observed (Reichenberg et al., 2001; Wright et al., 2005). It has been found out that IL-1β and TNF-α partially influence synthesis and metabolism of serotonin, by stimulation of indoleamine 2,3-dioxygenase (i.e., an enzyme involved in tryptophan metabolism) (Wichers and Maes, 2002) and by activation of the serotonin transporter SERT (Zhu et al., 2006). The pro-inflammatory cytokines activate the HPA axis and promote CRF secretion (Jeon and

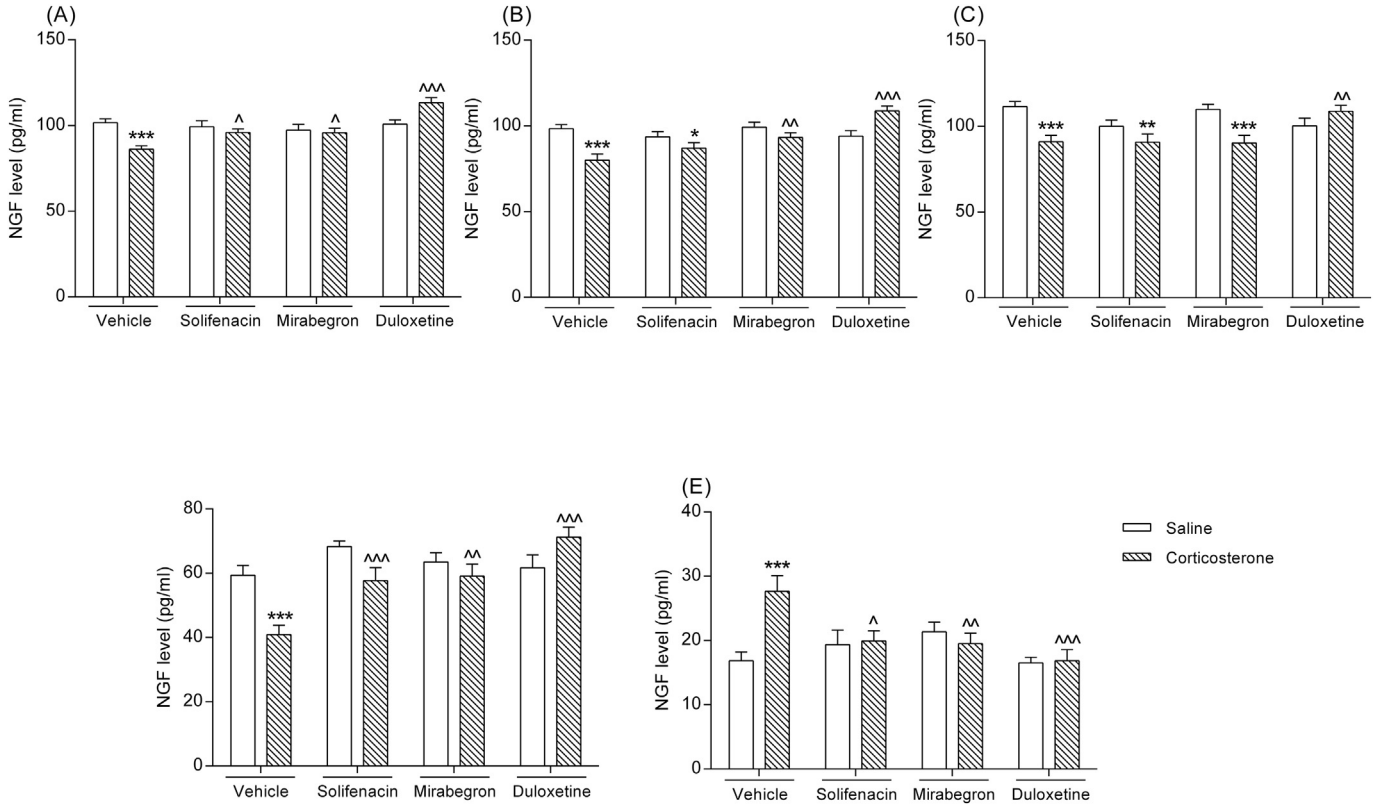

Fig. 6. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on levels of nerve growth factor (GNF) in the (A) hippocampus, (B) prefrontal cortex, (C) Barrington's nucleus, (D) urinary bladder and (E) urine of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.). The values represent the mean + SEM (n = 10–12 rats per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus vehicle-treated group, ^p < 0.05, ^^p < 0.01, ^^^p < 0.001 versus corticosterone-treated group (Bonferroni's post hoc test).

Kim, 2016). In our studies we also detected significant abnormalities in the CRF system. Corticosterone administration considerably increased CRF levels in the bladder, urine, and the brain areas involved in voiding control and development of depression, i.e. the amygdala, hippocampus, prefrontal cortex, and Barrington's nucleus. The CRF system seems to be one of the most essential common denominators that link depression and OAB. Disturbances in the CRF system are observed in depressed patients (Nemeroff et al., 1984; Banki et al., 1987; Merali et al., 2004) and they play a significant role in urinary bladder overactivity (LaBerge et al., 2006). Increased CRF levels in CSF were detected in suicide victims (Arato et al., 1989) and subjects with depression (Nemeroff et al., 1984; Banki et al., 1987; Hartline et al., 1996). Elevated CRF levels may lower the micturition threshold, micturition volume, and intercontraction intervals, whereas the blockage of the CRF system by their antagonists results in reduced DO in animal models (Klausner et al., 2005). Corticosterone-treated rats also presented decreased levels of BDNF and NGF in the brain and urinary bladder samples along with their elevated levels in urine. Similarly to our result, urinary BDNF and NGF levels are higher in patients with OAB (Bhide et al., 2013). It seems that abnormalities in urinary BDNF are a more sensitive marker of OAB than NFG in subjects without other disorders of the lower urinary tracts (Wang et al., 2014). By contrast, elevated levels of BDNF and NGF were detected in the brains of depressed people and suicide victims (Mondal and Fatima, 2018), which also was in line with our outcomes.

Results of the present study demonstrated that both solifenacin and mirabegron act mainly via peripheral pathways in OAB. Though an acute administration of solifenacin (0.03 mg/kg) and mirabegron (1 mg/kg) reversed the symptoms of DO (Wrobel et al., 2017), the 3-day post-treatment interval applied in our prolonged study abolished these effects. Only a partial decrease of the elevated FNVC values and a partial increase of the reduced ICI values were observed in solifenacin-treated animals. Likewise, only a partial normalization of both diminished levels of CB and augmented values of ANVC, DOI, and FNVC was detected in mirabegron-treated rats. 72 h after discontinuation of solifenacin or mirabegron treatment we did not observe any positive changes in the corticosterone-induced depressive-like behaviour of animals as well as any reversal of inflammation signs or abnormalities of the levels of CRF (except for a partial decrease of the bladder CRF levels in the case of solifenacin therapy). In the acute studies (Wrobel et al., 2017), neither solifenacin nor mirabegron reduced the elevated levels of CRF or exhibited an antidepressant potential. However, the outcomes of experiments by Sun et al. (2019), Stemmelin et al. (2010) or Overstreet et al. (2008) suggested that both antagonism of M_1/M_3 receptors and agonism of β3-adrenergic receptors could be promising novel strategies in the treatment of depression. An acute intraperitoneal (i.p.) injection of an anti-cholinergic agent penehyclidine hydrochloride (0.3–3 mg/kg) produced a rapid antidepressant-like effect in the FST and the tail suspension test in ICR mice, whereas a 4-day administration of this agent (1 mg/kg/day, i.p.) ameliorated anhedonia-like behaviour in animals subjected to the chronic unpredictable mild stress (Sun et al., 2019). On the other hand, an agonist of β3-adrenergic receptors – amibegron (0.3–3.0 mg/kg/day, i.p. for 14 days), reduced immobility of the Flinders Sensitive Line rats in the FST (Overstreet et al., 2008) and it exerted positive effects in the chronic mild stress model of depression in mice (3 mg/kg/day, i.p. for 33 days) (Stemmelin et al., 2010).

Interestingly enough, the 3-day post-treatment interval did not abolish solifenacin and mirabegron effects on normalization of the neurotrophin levels. Introduced treatment elevated the reduced BDNF levels in the urinary bladder and diminished the increased BDNF levels in urine. Moreover, solifenacin and mirabegron reversed the corticosterone-induced abnormalities of NGF values in the hippocampus,

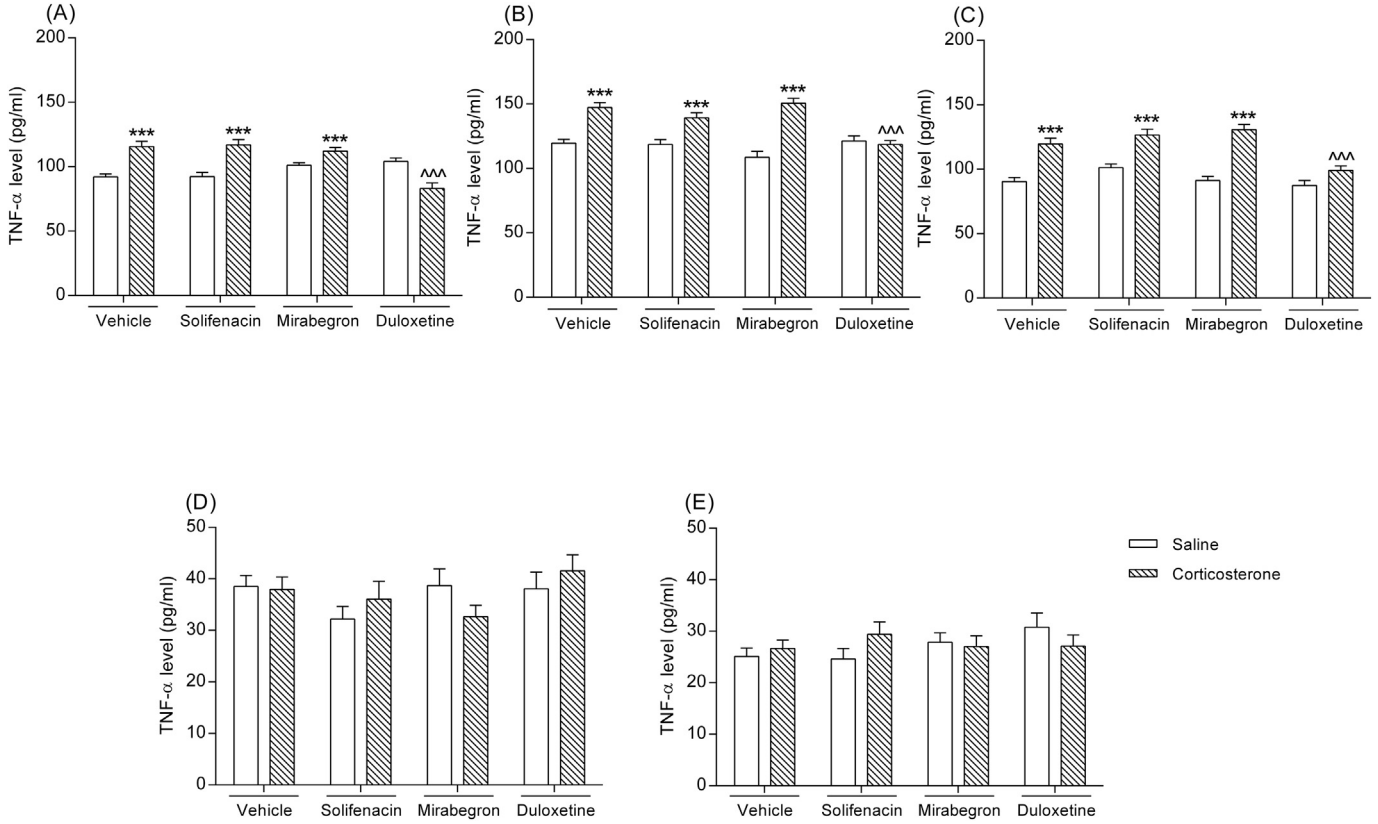

Fig. 7. Influence of the 14-day intravenous administration of solifenacin (0.03 mg/kg/day), mirabegron (1 mg/kg/day), and duloxetine (1 mg/kg/day) on levels of tumor necrosis factor α (TNF-α) in the (A) hippocampus, (B) prefrontal cortex, (C) Barrington's nucleus, (D) urinary bladder and (E) urine of rats subjected to 14-day corticosterone treatment (20 mg/kg/day, s.c.). The values represent the mean + SEM (n = 10–12 rats per group). ***p < 0.001 versus vehicle-treated group, ^^^p < 0.001 versus corticosterone-treated group (Bonferroni's post hoc test).

amygdala, urinary bladder, and urine. Liu et al. (Liu et al., 2009) suggested that urinary NGF could be an indicator of effectiveness of antimuscarinic treatment. Improvement of OAB symptoms due to tolterodine therapy was accompanied by a significant drop in urinary NGF levels, whereas failure with solifenacin treatment did not influence NGF values in urine (Liu et al., 2011). Our result did not confirm this concept, as quite normalized urinary NGF levels in solifenacin-treated rats were accompanied by only partially reversed changes in DO symptoms.

We confirmed the suppositions of Thor and Katofiasc (1995) that the central pathways are responsible for the inhibitory effects of duloxetine on the activity of the bladder detrusor, since the positive effects of this SNRI on cystometric parameters were noted even 72 h after discontinuation of the treatment. Normalization of DOI levels is particularly encouraging, since DOI is regarded as a more precise parameter describing bladder contraction than BC, BP, ICI, MVP, ANVC, or FNVC. Its increase allows to determine the intensity of DO (Wróbel and Rechberger, 2017b; Wróbel and Rechberger, 2017a). Another encouraging observation from our study was the fact that the 14-day administration of duloxetine did not influence PVR, though urinary retention can be observed after SNRIs (Carvalho et al., 2016). Furthermore, Solmaz et al. (2017) demonstrated that antidepressant drugs (including escitalopram, sertraline, fluoxetine, paroxetine, or venlafaxine) may increase the prevalence of OAB and intensify its symptoms. But in experiments by Schwen et al. (2013), an intravenous administration of duloxetine (3 mg/kg) increased bladder capacity and inhibited bladder overactivity induced by 0.25% solution of acetic acid. Two i.p. doses of duloxetine (2 mg/kg) prolonged the first void latency, reduced a number of urine spots, and reduced the urine volume in the OAB model in mice (Redaelli et al., 2015). Similarly, in a randomised placebo-controlled clinical trial, Steers et al. (2007) demonstrated that the treatment with duloxetine (given at a dose of 80 mg/day for 4 weeks and then elevated to 120 mg/day for 8 weeks) had a better therapeutic efficacy than placebo in women with OAB symptoms. It significantly decreased both the number of voiding episodes and the number of urinary incontinence episodes, and prolonged the daytime voiding interval. Di Rezze et al. (2012) reported that duloxetine reduced postmicturition residual volume when compared to placebo-treated patients. Duloxetine elevates levels of serotonin and noradrenalin, but its affinity towards serotonin and noradrenaline receptors is not clinically significant. According to the literature data (Di Rezze et al., 2012) effectiveness of duloxetine in the stress urinary incontinence is due to blockage of the reuptake of serotonin and noradrenaline at the presynaptic motoneurons in the Onuf's nucleus. The Onuf's nucleus is located in the sacral segments of the spinal cord. It consists of motoneurons that control the contracting activity of the urethral sphincter. By elevation of serotonin and noradrenaline levels, duloxetine allows continuous stimulation of the α1-adrenoceptors and serotonergic receptors at the post-synaptic side, which in turn activates the glutamatergic transmission and facilitates contraction of the urethral sphincter. Additionally, the direct serotonergic inhibition on sensory afferents, which results in decreased bladder activity also contributes to the observed effects (Burgard et al., 2003). Mechanisms responsible for duloxetine effects on the bladder capacity are also controlled at the spinal level, and they are dependent on the non-selective serotonergic pathways (Di Rezze et al., 2012).

Duloxetine normalized CRF, cytokines, BDNF, and NGF levels in all tested samples, which was not surprising. Antidepressant drugs are known to have an inhibitory effect on the up-regulated CRF system (Binder and Nemeroff, 2010), and the elevated CRF values in CSF are at least partially reduced after antidepressant treatment (De Bellis et al., 1993; Veith et al., 1993; Heuser et al., 1998). Interferon-α-induced depression, associated with elevated levels of pro-inflammatory

cytokines, was successfully treated by antidepressants (Musselman et al., 2001; Su et al., 2014). Similarly, lower levels of BDNF and NGF are increased as a consequence of antidepressant treatment (Mikoteit et al., 2014; Hassanzadeh and Rahimpour, 2011). The outcomes of the present study are generally in line with observations of Wang et al. (2015) who reported the first case of an effective duloxetine therapy in a female patient with OAB and depression, who had not responded to citalopram and had experienced side effects due to fluoxetine and imipramine treatment. After several months of taking duloxetine (up to 60 mg/kg), both depression and OAB symptoms improved.

In summary, we found out that the corticosterone-induced model of DO and depression is accompanied by: (1) increased brain levels of the pro-inflammatory cytokines, such as IL-1β and TNF-α, (2) elevated brain, bladder, and urine values of CRF, (3) reduced brain and bladder levels of neurotrophins, like BDNF and NGF, and (4) increased urine values of BDNF and NGF. We also demonstrated that solifenacin and mirabegron act mainly via peripheral pathways, whereas the central pathways are responsible for effects of duloxetine on both depression and DO. 72 h after discontinuation of duloxetine treatment, its beneficial effects were still detectable. Duloxetine seems to have a potential to become a new treatment option for patients with OAB co-existing with depression.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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