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RESEARCH ARTICLE

The effects of agomelatine, fluoxetine, and sertraline on rat bladder contraction *in vitro*

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ABSTRACT

Objective: This study aimed to determine the potential effects of three popular antidepressants: agomelatine, fluoxetine, and sertraline on *in vitro* rat bladder contraction responses, and to investigate their contribution to overactive bladder syndrome.

Method: Thirty-two adult male Wistar albino rats, weighing between 300–350 g, were randomly divided into four groups (Control, Agomelatine, Fluoxetine, Sertraline). After cervical dislocation, the bladders were promptly removed, cut into 3–4-millimeter strips, and suspended in an isolated organ bath at a tension of 1 gram. Contractions were induced by acetylcholine (ACh) at a concentration of 10^{-5} M. Cumulative doses of agomelatine, fluoxetine, and sertraline (ranging from 10^{-8} to 10^{-3} M) were administered to the organ bath chambers. The least squares means were compared using the Tukey-Kramer post-hoc test to compare the tension values of the groups at different time points.

Results: The inhibition of rat bladder contractions was statistically significant at agomelatine doses of 10^{-7} M ($p=0.0413$), 10^{-6} M ($p=0.033$), 10^{-5} M ($p=0.003$), and 10^{-4} M ($p<0.001$), with a statistically significant recontraction response noticed after the agomelatine dose of 10^{-3} M ($p<0.001$). Cumulative fluoxetine doses at 10^{-7} M ($p=0.0182$), 10^{-6} M ($p=0.0012$), and 10^{-5}, 10^{-4}, 10^{-3} M (all at $p<0.001$), along with sertraline doses at 10^{-5} M ($p=0.0096$), 10^{-4} M ($p=0.001$), and 10^{-3} M ($p<0.001$), also significantly inhibited contraction.

Conclusion: Agomelatine, fluoxetine, and sertraline were found to exhibit inhibitory effects on bladder contraction in a dose-dependent manner.

Keywords: Overactive bladder, contraction, agomelatine, fluoxetine, sertraline

INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by urgency and urinary incontinence without local pathology, hormonal cause, or an infection (1). OAB results from excessive contraction of the detrusor muscle or increased bladder sensation. Some studies have suggested that the relaxation of the sphincter, as evidenced by urethral pressure measurements during bladder filling, can lead to a squeezing sensation, with afferent neurons also contributing to this sensation (2). Bladder relaxants can be beneficial in alleviating symptoms of an overactive bladder and reducing urinary incontinence (3). Antidepressant drugs are known to inhibit the bladder via their antimuscarinic effects (4). Antidepressants generally function by blocking the reuptake of certain neurotransmitters from the nerve endings and other neurotransmitter receptors. The receptors most affected by this blockade are muscarinic (acetylcholine, ACh), histaminic, α adrenergic, dopaminergic, and serotonergic receptors (5).

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The serotonin system is widespread in the brain and comprises a large number of receptor types. Serotonin release in the body increases with mechanical stretching and efferent vagal stimulation. Serotonin increases the contraction of the bladder's detrusor muscle (6). It serves as a modulator that maintains the balance between dopamine, noradrenaline, and Gamma-Aminobutyric Acid (GABA) (7). Serotonin is one of the most crucial neurotransmitters of the central and peripheral nervous systems (8,9).

Although the antidepressant activities of Selective Serotonin Reuptake Inhibitors (SSRIs) are generally uniform, they differ in terms of half-life, age-related metabolic changes, linearity of plasma levels, and pharmacokinetic changes (10). The therapeutic mechanism of SSRIs is based on the differential impacts on the 5-Hydroxytryptamine (5-HT) system. SSRIs are thought to function by slowing the reuptake of neurotransmitter molecules (especially serotonin) by presynaptic neurons. In this way, serotonin molecules can activate postsynaptic neurons more effectively by staying in the synaptic gap longer than usual (11). Serotonin induces contraction in the bladder muscle (12). This effect is exerted through direct muscular action or by stimulating autonomic innervation, mediated by 5-HT2 serotonin receptors. The 5-HT1 receptors are located both presynaptically and postsynaptically in the bladder. 5-HT2 receptors increase the levels of inositol triphosphate (IP3) and diacylglycerol (DAG) in tandem with phospholipase C. 5-HT3 receptors interact with sodium channels in the membrane, inducing a contraction effect in the bladder (13).

Fluoxetine, apart from being an SSRI and a 5-HT2C antagonist, also acts as a norepinephrine and dopamine disinhibitor (14). It is one of the most frequently prescribed drugs for the treatment of depression (15). Fluoxetine is metabolized in the liver into its active metabolite, norfluoxetine. Due to its noradrenaline and dopamine disinhibitory effects, it increases the release of dopamine and norepinephrine (NE) from the prefrontal cortex (16).

Sertraline, a naphthylamine derivative, is among the most important inhibitors of 5-HT reuptake. It stands as the most selective 5-HT blocker in terms of noradrenaline reuptake. Sertraline has a weak effect on dopamine reabsorption (17,18). By influencing the serotonin reuptake pump, it increases the amount of serotonin in the synaptic cleft. It notably reduces the sensitivity of 5-HT1A receptors.

Furthermore, sertraline is a potent, selective 5-HT2C reuptake inhibitor. It inhibits Na+ channels at presynaptic nerve endings, promoting K+ ions to flow out of the cell. Its effect on serotonin reuptake is approximately five times greater than that of agomelatine (19).

Agomelatine is a melatoninergic antidepressant directed toward targets other than monoamines, such as the melatonin system (20). Compared to other antidepressants, agomelatine exhibits fewer side effects (21). It has an agonistic effect on muscarinic receptors (M1-M2) and antagonizes serotonin 5-HT2C (22,23).

Agomelatine does not influence the release of serotonin and shows no affinity for muscarinic, adrenergic, noradrenergic, or dopaminergic transporters (24). Its lack of affinity for muscarinic, histaminergic, and 5-HT1A receptors reduces the side effects associated with these receptors. Additionally, side effects caused by monoamine increases are less prevalent than with SSRIs and serotonin-noradrenaline reuptake inhibitors (SNRIs) (25).

While SSRIs do not demonstrate significant advantages over each other in effectiveness, they exhibit variations in drug interactions due to their side effects, usage patterns, and different effects. All known antidepressants enhance monoamine neurotransmission primarily by blocking one or more reuptake transporters for serotonin, norepinephrine, and/or dopamine. Numerous treatment methods have been explored in OAB syndrome, with antimuscarinic agents being the principal therapeutic drug. However, these agents exhibit high side effect profiles and low efficacy (26), prompting continued exploration for improved OAB treatments.

Moreover, antidepressants cause different side effects in the urinary system. Urinary retention (UR) is a condition characterized by the impaired emptying of the bladder, resulting in residual urine retention. In some instances, using sertraline and fluoxetine has resulted in acute urinary retention (27). UR is seen in patients on antipsychotic and antidepressant medications with no apparent underlying urological cause. It occurs in 0.025% of patients on selective serotonin reuptake inhibitors and patients on typical antipsychotics and selective noradrenaline reuptake inhibitors. Most case reports indicate an improvement in UR upon medication discontinuation or dose reduction. Antipsychotics and antidepressants interact with the urinary system in many ways (28).

As OAB symptom severity increases, patient stress/anxiety levels may rise. Prolonged disease duration can lead to depression. Few studies have specifically investigated the relationship between psychological stress and urinary symptoms in OAB patients.

Agomelatine, fluoxetine, and sertraline are commonly prescribed antidepressants, often chosen to mitigate some symptoms of OAB syndrome. However, when considering the side effects of these drugs, studies addressing which antidepressants should be selected are limited. These three antidepressants have numerous effects, but their dose-related impacts on bladder smooth muscle structure remain unclear. Through this study, we aim to present a different perspective on selecting antidepressants for preventing urgency and urinary incontinence in OAB patients.

In this study, we aim to identify any potential differences in cumulative concentrations to discern the effects of agomelatine, fluoxetine, and sertraline, which are commonly prescribed for OAB syndrome, on bladder smooth muscle contractility.

METHOD

Ethical Approval

The protocols for the animal experiments were approved by the Experimental Medicine Application and Research Center Local Ethics Committee of Necmettin Erbakan University (approval date: 31.08.2018, number: 2018-030). The Scientific Research Project Board funded study 81318015, and the project was officially completed on 11.11.2019. The project was conducted in the Smooth Muscle Laboratory of the Medical Faculty, Department of Physiology.

Experimental Procedure

Rats were housed in plastic cages where they could move freely. Food and water were provided ad libitum. In standard laboratory conditions, the animals were kept at room temperature (22±1°C) under a 12-hour light/dark cycle. All animal procedures adhered to the ''Guide for Care and Use of Laboratory Animals'' (NIH US publication No 85–23, revised 1985) recommendations. Adult male Wistar albino rats (16 weeks old, 300–350 grams) were utilized for the study. A total of 32 rats were randomly divided into four groups.

After the rats were sacrificed by cervical dislocation under mild ether anesthesia, their abdomens were opened with a median line incision, and the urinary bladders were carefully removed. Bladder tissue samples were placed into Petri dishes containing Krebs solution. Bladder strips (2x10 mm) were prepared from the tissues. The prepared strips were placed in the apparatus in the glass chambers of the isolated organ bath. Bladder strips were suspended in a 10 ml chamber filled with Krebs-Henseleit solution (composed of (mM): NaCl 119, KCl 4.70, $MgSO_4$ 1.50, KH_2PO_4 1.20, $CaCl_2$ 2.50, $NaHCO_3$ 25, glucose 11) under a resting tension of 1 g, maintained at 37 °C, and aerated with 95% O_2 and 5% CO_2. After suspending the strips, they were washed at 15-minute intervals for 45 minutes to allow for the elimination of anesthetic agents and the formation of spontaneous contractions. After the stabilization period of spontaneous contractions, ACh was administered into the glass chambers of the organ bath at a dose of 10^{-5} M (100 µl). The ACh administration induced spontaneous contractions.

Changes in the isometric tension of bladder strips were recorded using a four-channel force-displacement transducer (May Iobs 99 Isolated Tissue Bath Stand Set Integrated Tissue Bath System, Commat, Ankara, Turkiye). Distilled water circulated in the thermos-circulator (May Wbc 3044-Pr Heating Circulator) on the outer walls of all chambers of the isolated organ bath system, which had a double-wall structure and four chambers. This water maintained the Krebs solution in the chamber at the required temperature. The liquid-gas transport apparatus circulated the Krebs solution throughout the organ bath, allowing the mixture to reach the hoppers.

The experiments were organized into four groups:

Group 1 (Control group, N=8): Contractions were induced by 10^{-5} M ACh administration to isolated organ bath chambers.

Group 2 (Agomelatine group, N=8): After contractions were induced by 10^{-5} M ACh, cumulative agomelatine (10^{-8} to 10^{-3} M) was administered to all chambers.

Group 3 (Fluoxetine group, N=8): After contractions were induced by 10^{-5} M ACh, cumulative fluoxetine (10^{-8} to 10^{-3} M) was administered to all chambers.

Group 4 (Sertraline group, N=8): After contractions were induced by 10^{-5} M ACh, cumulative sertraline (10^{-8} to 10^{-3} M) was administered to all chambers.

Agomelatine (S-20098, N-[2-(7-methoxy-1-naphthalenyl) ethyl]-acetamide) (10.92 mg), fluoxetine hydrochloride, (±)-N-Methyl-γ-[4-(trifluoromethyl) phenoxy] benzenepropanamine hydrochloride, LY-110, 140 hydrochloride, Prozac, Fluoxetine hydrochloride) (10.92 mg), and sertraline hydrochloride [(1S, 4S)-4-(3, 4-dichlorophenyl)]-

1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride) (10.92 mg) were dissolved in distilled water. The prepared agomelatine, fluoxetine, and sertraline solutions were separated into small plastic tubes and stored at +4°C until application to the organ bath. The tubes were wrapped with aluminum foil, as the solutions were light-sensitive. Care was taken to protect against light during the experiment. The bladder strips obtained from 32 rats were placed in the isolated organ bath. Contractions were recorded by applying 1 gram of tension to the strips. The tension level was kept constant throughout the experimental period. The strips were washed every 15 minutes, and bladder strips showing spontaneous contractions were induced with 10^{-5} M ACh after a 45-minute adaptation period. No interventions were made during the procedure. After a 15-minute wait, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M of agomelatine, fluoxetine, and sertraline were added cumulatively at 10-minute intervals, sequentially. The effects were recorded.

Statistical Analysis

Descriptive statistics were expressed as the arithmetic mean (AM)±standard error (SE) for the isometric tension values. A mixed-effects model was used to analyze the variation in tension values over time and between groups, including interaction terms (group × time). As a result of this model, the effects of the group, time, and group-time interaction were investigated. The least squares means were compared using the Tukey-Kramer post-hoc test to compare the tension values of the groups at different time points. Analyses were performed using the Statistical Analysis System (SAS) University Edition 9.4 program. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Administering of 10^{-5} M ACh to bladder smooth muscle increased muscle contractility (Fig. 1).

A dose-response curve of agomelatine on bladder muscle induced by ACh 10^{-5} M was obtained. Over time, agomelatine was observed to inhibit contractions. There was a statistically significant inhibition of contraction in the urinary bladder muscle due to agomelatine at a 10^{-8} M dose. This inhibition of rat bladder contractions was statistically significant with agomelatine doses of 10^{-7} M ($p=0.0413$), 10^{-6} M ($p=0.033$), 10^{-5} M ($p=0.003$), and 10^{-4} M ($p<0.001$). Interestingly, a statistically significant recontraction response was observed following the agomelatine dose of 10^{-3} M ($p<0.001$) (Fig. 2).

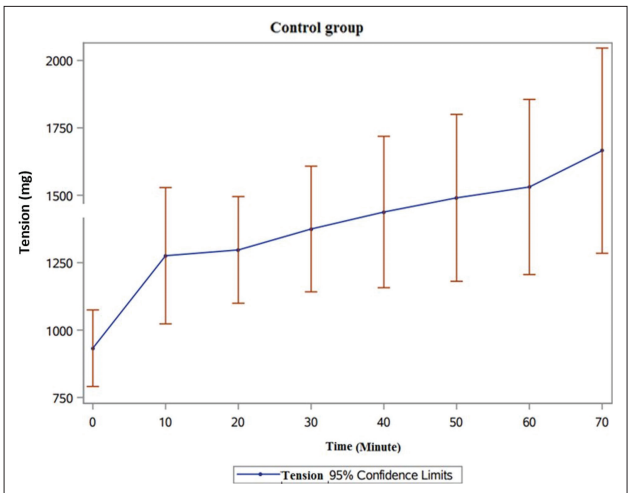

Figure 1. Effects of ACh (10^{-5} M) on bladder smooth muscle contraction (Group 1=Control group).

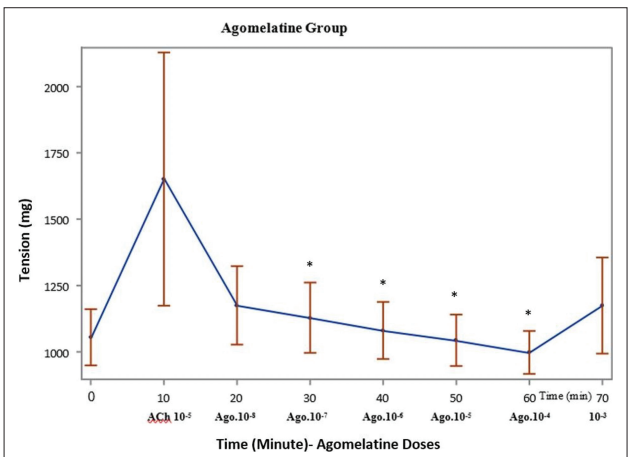

Figure 2. Effects of cumulative doses of agomelatine (10^{-8}–10^{-3} M) on ACh-induced (10^{-5} M) bladder smooth muscle contraction (Group 2=Agomelatine group) (*: $p<0.05$).

Contraction inhibition in the urinary bladder muscle was statistically significant at fluoxetine doses of 10^{-7} M ($p=0.0182$), 10^{-6} M ($p=0.0012$), 10^{-5}, 10^{-4}, 10^{-3} M ($p<0.001$) (Fig. 3, Tables 1, 2).

A significant contraction inhibition in the urinary bladder muscle was observed after a 10^{-8} M dose of sertraline ($p=0.6065$), and statistically significant inhibition responses were observed with 10^{-5} M ($p=0.0096$), 10^{-4} M ($p<0.001$), and 10^{-3} M ($p<0.001$) doses of sertraline (Fig. 4, Tables 1, 2).

The dose-response curves of agomelatine, fluoxetine, and sertraline were obtained in bladder smooth muscle induced by 10^{-5} M ACh. These three active substances, antidepressants, inhibited contractions in a dose-dependent manner over time. It was observed that only agomelatine increased

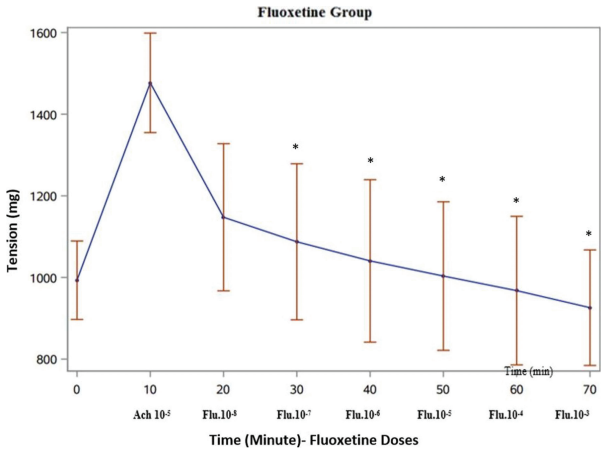

Figure 3. Effects of cumulative doses of fluoxetine (10^{-8}–10^{-3} M) on ACh-induced (10^{-5} M) bladder smooth muscle contraction (Group 3=Fluoxetine group) (*: p<0.05).

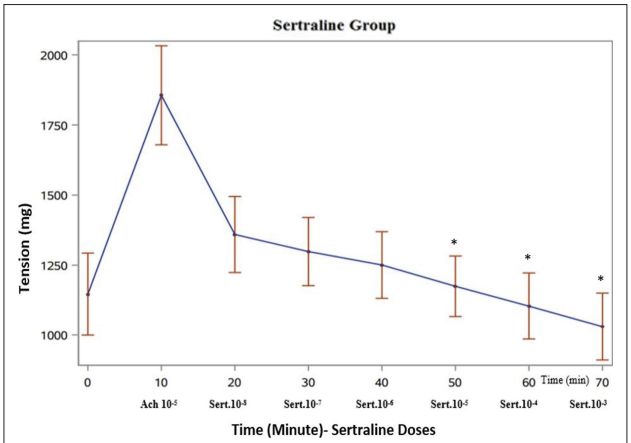

Figure 4. Effects of cumulative doses of sertraline (10^{-8}–10^{-3} M) on ACh-induced (10^{-5} M) bladder smooth muscle contraction (Group 4=Sertraline group) (*: p<0.05).

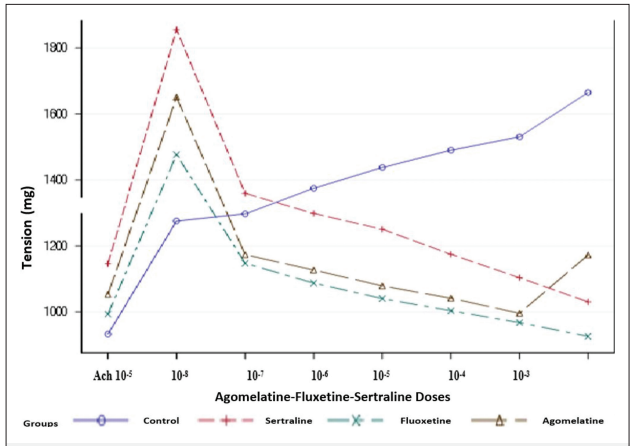

Figure 5. Comparison of agomelatine, fluoxetine, and sertraline effects on ACh-induced bladder smooth muscle contraction. Agomelatine increased contraction after a 10^{-3} M dose (p<0.001).

contractions in bladder smooth muscle after a 10^{-3} M dose (Fig. 5, Table 1).

While agomelatine, fluoxetine, and sertraline were effective in contraction inhibition, they did not create a statistically significant difference among themselves except at a 10^{-3} M agomelatine-fluoxetine dose (p=0.0421) (Table 3, 4) (*: p<0.05).

DISCUSSION

In this study, the effects of agomelatine, sertraline, and fluoxetine on muscle contraction in rat bladder smooth muscle tissues were investigated. The study showed that cumulatively increased doses of agomelatine, sertraline, and fluoxetine produced dose-dependent relaxation. Given that these antidepressant drugs reduce bladder smooth muscle contraction responses

Table 1: The effect of cumulative agomelatine, fluoxetine, and sertraline dose administration on bladder smooth muscle contractility *in vitro*

	Control group		Agomelatine group		Fluoxetine group		Sertraline group	
Cumulative dose	**Average tension**	**Standard deviation**	**Average tension**	**Standard deviation**	**Average tension**	**Standard deviation**	**Average tension**	**Standard deviation**
Spontaneous contraction	932.79	169.63	1053.16	127.12	993.27	114.80	1146.34	175.51
ACh 10^{-5} M (50. min)	1275.86	302.30	1650.86	572.46	1476.76	145.57	1855.91	211.23
10^{-8} M (65. min)	1297.12	236.62	1173.42	177.39	1147.52	215.57	1359.42	162.29
10^{-7} M (75. min)	1374.82	278.72	1127.05	158.97	1087.44	228.63	1298.56	145.41
10^{-6} M (85. min)	1437.79	335.33	1078.96	128.91	1040.60	238.06	1250.70	142.22
10^{-5} M (95. min)	1490.41	370.33	1041.54	116.22	1003.45	217.73	1174.74	129.08
10^{-4} M (105. min)	1530.64	388.48	995.86	196.74	967.74	217.61	1103.84	141.47
10^{-3} M (115. min)	1665.29	455.08	1172.76	217.36	925.99	169.35	1030.48	143.37

Ach: Acetylcholine.

Table 2: Statistical evaluation of cumulative agomelatine, fluoxetine, and sertraline doses (10^{-8}–10^{-3} M)

Cumulative dose	Agomelatine	Fluoxetine	Sertraline
10^{-8} M	0.362	0.2163	0.6065
10^{-7} M	**0.0413***	**0.0182***	0.5280
10^{-6} M	**0.033***	**0.0012***	0.1225
10^{-5} M	**0.003***	**<0.001***	**0.0096***
10^{-4} M	**<0.001***	**<0.001***	**<0.001***
10^{-3} M	**<0.001***	**<0.001***	**<0.001***

*: p<0.05.

Table 3: Group-time comparison in agomelatine, fluoxetine, and sertraline groups

Effect	Num DF	Den DF	F value	Pr>F
Group	3	196	3.15	0.0262
Time	7	196	41.82	**<0.0001***
Group*Time	21	196	14.22	**<0.0001***

*: p<0.05.

Table 4: Comparison of p-values in agomelatine, fluoxetine, and sertraline groups

Dose	Agomelatine -Sertraline	Sertraline -Fluoxetine	Agomelatine -Fluoxetine
10^{-5} M	0.2709	0.1572	0.7525
10^{-4} M	0.3718	0.2606	0.8159
10^{-3} M	0.2397	0.3874	**0.0421***

*: p<0.05.

- a finding that stands in contrast to other studies- they can be recommended during the treatment of OAB syndrome to reduce symptoms that significantly affect the human quality of life, such as feelings of urgency and frequent urination.

Only 50–60% of treatment success has been achieved with antimuscarinics, which are considered effective in treating OAB. Consequently, researchers are working to find a more definitive diagnostic method. In OAB syndrome, patients have to cope with issues such as sudden urgency and sudden urinary incontinence (29). Cholinergic and adrenergic mechanisms play a role in bladder innervation. Structural changes such as bladder outlet obstruction, loss of bladder nerve fibers, and hypertonia of smooth muscle cells in the bladder cause various symptoms of OAB syndrome (30,31).

ACh is released from certain regions in the detrusor muscle, causing concentration-dependent contractions (32). Nonneuronal ACh can regulate bladder tone and cause OAB contractions. If ACh neuronal release is low during storage, antimuscarinic drugs may show greater efficacy (33). Serotonin produces concentration-dependent contractions in the bladder detrusor muscle. SSRIs inhibit serotonergic transporters and increase the level of serotonin in the synaptic cleft (34). It has been suggested that serotonergic transporters may have important effects on these inhibited responses in bladder smooth muscle contractions inhibited by SSRIs (35).

Chronic administration of antidepressant drugs in rats has been shown to inhibit isolated rat smooth muscle. It has been reported that the peripheral effects of antidepressants, apart from serotonin reuptake inhibitors, which are responsible for central effects, may effectively inhibit Ca^{2+} entry or noradrenaline reuptake (36). In studies involving sertraline and fluoxetine, it has been reported that these agents reduce smooth muscle contractions, and this effect is due to the inhibition of Ca^{2+} entry independent of adrenergic receptors (37).

The hypercontractile responses of detrusor strips to carbachol, electrical field stimulation (EFS), and potassium chloride (KCl) were abolished with fluoxetine and sertraline. The results of this study suggest that hypercontractility was abolished by chronic treatments of fluoxetine and sertraline at antidepressant doses by decreasing post-receptor-mediated events (38).

The potential inhibitory effects of 18 antidepressants on ACh-induced contractions in guinea pig urinary bladder smooth muscle were investigated. ACh-induced contraction was competitively antagonized within clinical dose ranges by tricyclic antidepressants (imipramine, amitriptyline, trimipramine, clomipramine, nortriptyline, and amoxapine), maprotiline (a tetracyclic antidepressant), and mirtazapine (a noradrenergic and specific serotonergic antidepressant). ACh-induced contraction was also significantly inhibited by mianserin (a tetracyclic antidepressant), paroxetine, sertraline, and duloxetine (a serotonin noradrenaline reuptake inhibitor). However, ACh-induced contractions were not significantly affected by fluvoxamine and escitalopram (SSRIs), milnacipran (an SNRI), trazodone (a serotonin 5-HT2A receptor antagonist), sulpiride (a dopamine D2 receptor antagonist), or aripiprazole (a dopamine partial agonist). These findings suggest that some antidepressants may affect voiding dysfunction as decreased urinary bladder smooth muscle contractility by inhibiting muscarinic receptors (39).

In a study of 26 antipsychotics, six (chlorpromazine, levomepromazine (phenothiazines), zotepine (a

thiepine), olanzapine, quetiapine, clozapine (multi-acting receptor targeted antipsychotics)) competitively inhibited ACh-induced contractions. Additionally, 11 antipsychotics (perphenazine, fluphenazine, prochlorperazine (phenothiazines), haloperidol, bromperidol, timiperone, spiperone (butyrophenones), pimozide (a diphenylbutylpiperidine), perospirone, blonanserin (serotonin-dopamine antagonists), and asenapine) significantly suppressed ACh-induced contraction; however, this suppression occurred at concentrations substantially exceeding clinically achievable blood levels. The remaining nine antipsychotics (pipamperone, sulpiride, sultopride, tiapride, nemonapride, risperidone, paliperidone, aripiprazole, and brexpiprazole) did not inhibit ACh-induced contractions at concentrations up to 10^{-5} M. The most significant factor causing drug-induced urinary disorders is a decrease in urinary bladder smooth muscle contraction induced by the anticholinergic action of these therapeutics. However, the anticholinergic action-associated inhibitory effects of antipsychotics on urinary bladder smooth muscle contraction have not been sufficiently assessed (40).

We investigated whether the potential inhibitory effects of clinically used hypnotic drugs on ACh-induced contractions in rat bladder smooth muscle could cause voiding dysfunction. Most clinically used hypnotics do not exhibit anticholinergic action-mediated suppression of urinary bladder contraction and subsequent dysuria. However, inhibitory actions against ACh-induced urinary bladder contraction were found to be exerted by flurazepam (a benzodiazepine), suvorexant (an orexin receptor antagonist), and diphenhydramine (a histamine H1 receptor antagonist) (41).

A previous study showed that the incidence of OAB and the severity of OAB symptoms increased in men using antidepressants derived from venlafaxine and sertraline. This finding may be due to the pharmacological effects of serotonin-norepinephrine reuptake inhibitors at the molecular or individual level (42).

Another study examined whether treatment with sertraline reduced mice's bladder dysfunction caused by water avoidance stress. Bladders from stressed mice displayed an enhanced maximal contractile response to the muscarinic agonist carbachol, which was reduced to control levels by sertraline treatment. Spontaneous phasic contractions were not altered by stress but were significantly reduced in bladders from sertraline-treated animals relative to controls. These results suggest that managing voiding dysfunction caused by psychological stress may be aided by adding an SSRI such as sertraline (43).

In our study, different doses of agomelatine, fluoxetine, and sertraline administration decreased ACh-induced *in vitro* rat bladder smooth muscle contraction responses. As the drugs used for the study were SSRI family antidepressants, they demonstrated their effects by reducing the reuptake of neurotransmitter molecules (specifically, serotonin) by presynaptic neurons. It is hypothesized that since serotonin reuptake slows down, serotonin molecules stay in the synaptic gap longer and can activate postsynaptic neurons more.

Among the three antidepressant agents, fluoxetine decreased the bladder smooth muscle contraction responses the most. At the same time, agomelatine had the least dose-related safety. Certain cumulative doses of agomelatine decreased bladder smooth muscle contraction responses dose-dependently. However, after the highest dose (10^{-3} M) was administered, agomelatine increased isolated rat bladder smooth muscle contraction responses. This finding may explain why the use of a single daily dose of an agent with a short half-life of 2 hours has not been clarified. The possibility of exhibiting the opposite of the desired effect at higher doses can be considered.

There are some limitations in our study. Firstly, due to limited resources, we could not examine the mechanism underlying the relaxant effect of the three antidepressants at the cellular level. As the number of animals was limited, we could not observe the gender effect and the systemic effect of the drugs. We hope to investigate the underlying mechanism and systemic effect of antidepressants in future projects.

CONCLUSION

Agomelatine, fluoxetine, and sertraline, three popular antidepressant agents with frequent clinical use worldwide, dose-dependently inhibited ACh-induced isolated rat urinary bladder smooth muscle. Further studies are required to reveal the underlying mechanism.

Continuing studies, which will determine the different effects of the active components of antidepressant agents on rat bladder muscle *in vitro*, may provide support for their use in different clinical situations. This study can serve as a supportive step in the literature, supplementing various non-physiologic clinical conditions, such as overactive bladder syndrome. It may shed light on future bladder function-antidepressant agent studies.

Contribution Categories		Author Initials
Category 1	Concept/Design	Z.I.S.G., T.V.
	Literature review	Z.I.S.G., T.V.
	Data analysis/Interpretation	Z.I.S.G., T.V., R.O.K
Category 2	Drafting manuscript	Z.I.S.G., T.V.
	Critical revision of manuscript	Z.I.S.G., T.V., R.O.K
Category 3	Final approval and accountability	Z.I.S.G., T.V., R.O.K., H.S., E.F.U.

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