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Research Article
Venlafaxine Inhibits Detrusor Contractions in Rats: A Role for Extracellular Calcium

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Abstract

Background and Objective: Certain antidepressant drugs cause urinary incontinence while some of that are used to treat incontinence. This study was aimed to investigate the possible effects of venlafaxine in rat bladder detrusor muscle and the mechanisms involved in the inhibitory effect of contraction. **Methodology:** Strips of rat detrusor muscle were suspended in a perfusion organ bath. The contractile response to electrical field stimulation, acetylcholine and potassium chloride were determined after the addition of venlafaxine. To investigate the association of venlafaxine and other systems, it has been used nonselective beta blocker propranolol, nonselective serotonin receptor blocker methysergide, opioid receptor antagonist naloxone and non-selective alpha adrenergic receptor antagonist phentolamine. To demonstrate the role of calcium on the effect of venlafaxine on isolated detrusor muscle, diltiazem was used as a calcium channel blocker. For statistical analysis one-way analysis of variance (ANOVA) with the Tukey-Kramer post-hoc test was used. **Results:** Venlafaxine (5×10^{-4} M) inhibited the maximum contractile response to electrical field stimulation, acetylcholine and potassium by 73% ($p<0.001$), 36% ($p<0.001$), 87% ($p<0.001$), respectively. Propranolol, phentolamine, methysergide and naloxone did not change the inhibitory effect of venlafaxine on electrical field stimulation response. The maximum contractile response to 10^{-3} M acetylcholine was reduced by 76% of control ($p<0.001$) in the presence of 10^{-4} M diltiazem. The administration of venlafaxine (5×10^{-4} M) in combination with diltiazem (10^{-4} M) did not change the contractile responses of acetylcholine compared to diltiazem alone. **Conclusion:** It is concluded that venlafaxine inhibits rat detrusor muscle contraction via the inhibition of calcium influx from the extracellular space.

Key words: Acetylcholine, antidepressant, calcium, detrusor muscle contraction, *in vitro*, venlafaxine

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Antidepressants are the most prescribed drugs for the treatment of anxiety, obsessive-compulsive disorder and depression. These drugs are also used in the treatment of various urinary problems. Urinary incontinence is defined as involuntary urination and has been shown to affect up to 35% of community-residing women aged 70-75 years and 26% of community-residing men aged 85-89 years most of whom suffer from stress urinary incontinence[1]. Pharmacological management of incontinence includes administration of tricyclic antidepressants (TCA) with anticholinergic properties, which block presynaptic uptake of amine neurotransmitters and directly inhibit bladder muscle activity[2]. Imipramine, a tricylic antidepressant, has been shown to reduce bladder contractility with antagonistic effects on muscarinic receptors[3]. Duloxetine, a Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), has been shown to be effective in the treatment of stress urinary incontinence and overactive bladder in established clinical trials[4,5]. It was suggested that duloxetine increases the activity of the striated urethral sphincter, possibly through the inhibition of presynaptic reuptake of serotonin and noradrenaline in the Onuf's nucleus of the sacral spinal cord[6]. *In vitro* studies investigating the effect of antidepressants on the bladder detrusor muscle demonstrated that imipramine, maprotiline, mianserin, paroxetine and sertraline inhibited acetylcholine (ACh)-induced contractions in the detrusor smooth muscle, while fluvoxamine, escitalopram, milnacipran and sulpirid did not exhibit an inhibitory effect[7]. It was suggested that antidepressants that relax detrusor muscles may have antimuscarinic properties.

Venlafaxine (VFX) is an SNRI that is used in the treatment of depression. It inhibits serotonin reuptake, similar to Selective Serotonin Reuptake Inhibitors (SSRIs) and inhibits the reuptake of norepinephrine. There have been a few reports to suggest that VFX can cause urinary incontinence, possibly as a result of indirect potentialization of cholinergic neurotransmission in the bladder detrusor smooth muscle[8], while a study suggested that VFX may be used in the treatment of stress urinary incontinence[9]. However, the underlying mechanism of the effect of VFX on the bladder detrusor smooth muscle is unknown. Furthermore, there is no evidence that demonstrates the effect of venlafaxine and its mechanism of action on isolated detrusor muscles in rats. Therefore, this study was aimed to investigate the effect of VFX on isolated rat detrusor muscles and to determine the possible mechanisms of this effect.

MATERIALS AND METHODS

Adult Sprague Dawley rats of both sexes (250-300 g) were used. All procedures and protocols were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (NIH publication 865-23, Bethesda, MD, USA). Experiments were approved by the Local Animal Care and Use Committee. Rats were housed two per cage in a quiet, temperature and humidity-controlled room (22°C and 60±5%, respectively) in a 12 h light/dark cycle, receiving food and water ad libitum.

The urinary bladders were removed and dissected free from fat and adherent tissue. Muscle strips were sliced into 4×10 mm sections and transferred to organ baths containing Krebs Henseleit solution (NaCl 118 mM, KCl 5.6 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 1.2 mM, KH_2PO_4 0.9 mM, $NaHCO_3$ 25 mM, glucose 11 mM). The solution was continuously gassed with 95% O_2-5% CO_2 and maintained at 37.2°C and pH 7.4. Each preparation was threaded through a ring electrode (3 mm internal diameter, 1 cm apart) (MLA0305/8, ADInstruments, UK) and connected to a Grass S88 stimulator (Grass, USA). The lower end of the preparation was attached to a holder and the other end was attached to an isometric force transducer (MLT0201, ADInstruments, UK) coupled to a Quad Bridge amplifier (ML118, ADInstruments, UK) that was connected to a digital recorder PowerLab/4SP (ADInstruments, UK). All tissues were equilibrated for 1 h at 1 g resting tension.

Study protocol: Acethylcholine (ACh) (Sigma, USA) was administered in a cumulative manner (10^{-6}-10^{-3} M). The KCl (Sigma, USA) concentration was 80 mM. The frequency-response curves were constructed as follows: square wave pulses (100 V, 0.5 msec, 2-64 Hz). Venlafaxine (Egis Co., Turkey) (10^{-4}, 5×10^{-4}, 10^{-3} M) was dissolved in distilled water and added to the organ bath 10 min before administering ACh, KCl and Electrical Field Stimulation (EFS). To demonstrate the role of calcium on the effect of VFX on isolated detrusor muscle, diltiazem (10^{-4} M) was used as a calcium channel blocker.

To investigate the association of VFX and other systems, nonselective beta blocker propranolol (Sigma Aldrich, St. Louis, MO), nonselective serotonin receptor blocker methysergide (Sigma Aldrich, St. Louis, MO), opioid receptor antagonist naloxone (Sigma Aldrich, St. Louis, MO) and non-selective alpha adrenergic receptor antagonist phentolamine were used (Sigma Aldrich, St. Louis, MO).

Statistical analysis: In the isolated bladder detrusor muscle, the maximum contraction dose of ACh was determined to be

10^{-3} M in this study and this dose was used as the control. The ACh responses were considered to be 100% and VFX responses were calculated as percentage of the ACh-induced contraction response. The maximum contraction response of EFS was obtained at 32 Hz and VFX responses were calculated as percentage of the EFS-induced contraction response.

Results are presented as the Mean±SEM. Data analyses were performed using GraphPad Prism software (v6.0) (GraphPad Software Inc., San Diego, Calif., USA). Following the assurance of a normal distribution of data, one-way analysis of variance (ANOVA) with the Tukey-Kramer post hoc test was used for multiple comparisons. Values of $p<0.05$ were regarded as significant.

RESULTS

Effect of venlafaxine on EFS induced contractions: The contractions stimulated with EFS obtained from detrusor muscle strips were significantly increased at 2-64 Hz. Incubation with low concentrations of VFX (10^{-4} M) significantly reduced the maximum contractile response to EFS only at 32 and 64 Hz, while with VFX at concentrations of 5×10^{-4} and 10^{-3} M had significant inhibitory effect at all frequencies (2-64 Hz). The percent inhibition of EFS-induced contractions at 32 Hz was 36.42±12.05 ($p<0.05$), 73.01±4.73 ($p<0.001$) and 95.64±2.16 ($p<0.001$) at concentrations of 10^{-4} M, 5×10^{-4} M and 10^{-3} M VFX, respectively (n = 7) (Fig. 1, 2).

Effect of propranolol, phentolamine, methysergide and naloxone in combination with venlafaxine on EFS induced contractions: Propranolol (10^{-6} M), methysergide (10^{-6} M), naloxone (10^{-6} M) and phentolamine (10^{-6} M) preincubation did not alter the VFX (5×10^{-4} M) -induced inhibition of contractile response to EFS ($p>0.05$) (n = 7) (Fig. 3).

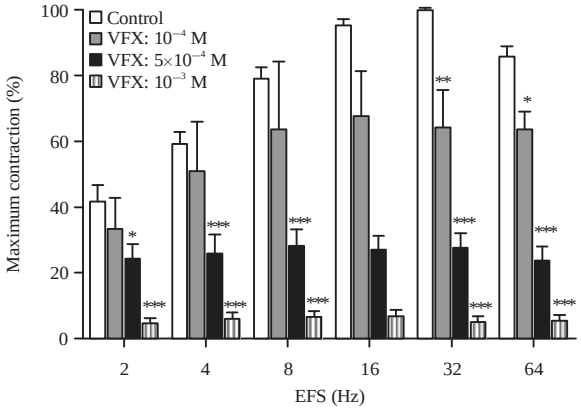

Fig. 1: Effect of VFX on the contractile responses of rat detrusor muscle to Electrical Field Stimulation (EFS)
*p<0.05, **p<0.01, ***p<0.001 compared to control group. Each point represents mean of 7 animals. Error bars show SEM

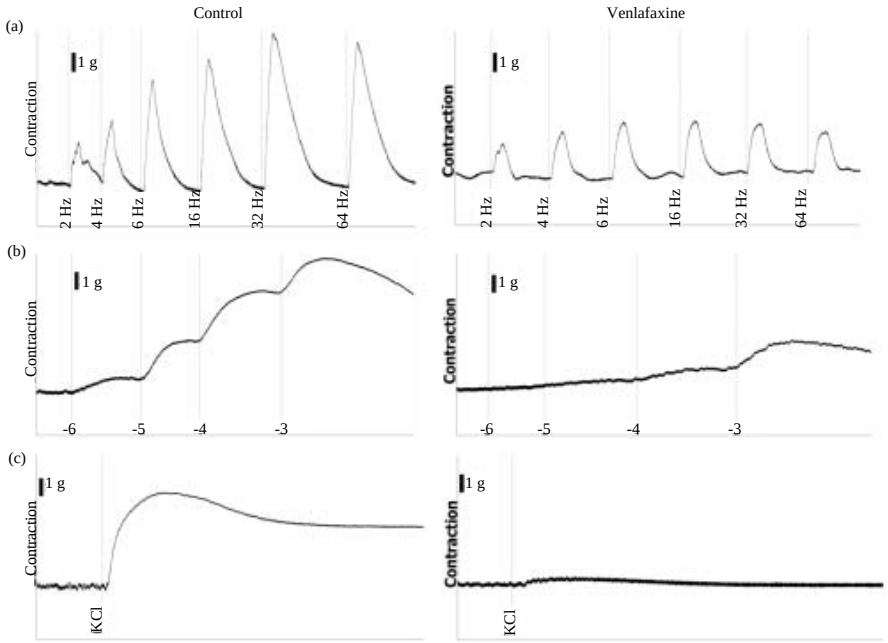

Fig. 2(a-c): Typical trace showing inhibitory effect of VFX on contractions produced by (a) Electrical Field Stimulation (EFS), (b) Acetylcholine and (c) KCl in isolated rat bladder

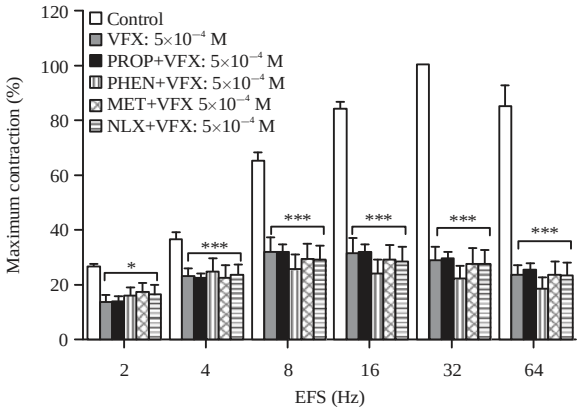

Fig. 3: Electrical field stimulation-induced contractions in isolated rat bladder

Effect of VFX (5×10^{-4} M) alone or in presence of combination of phentolamine (PHEN) (10^{-6} M), propranolol (PROP) (10^{-6} M), methysergide (MET) (10^{-6} M) and naloxone (NLX) (10^{-6} M). Each point represents mean of 7 animals. *p<0.05, ***p<0.001 compared to control group. Error bars show SEM

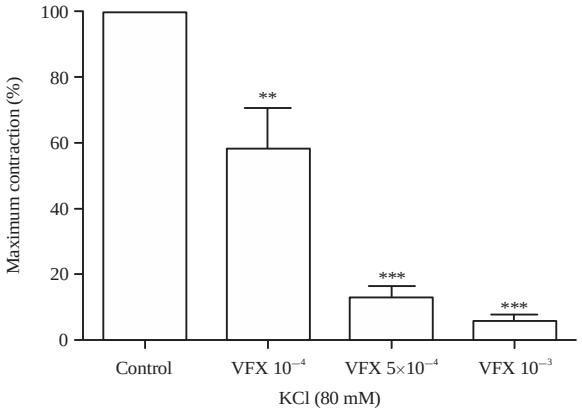

Fig. 4: Effect of VFX on the contractile responses of rat detrusor muscle to KCl (80 mM)

**p<0.01, ***p<0.001 compared to control group. Each point represents mean of 7 animals. Error bars show SEM

Effect of venlafaxine on KCl induced contractions: It was determined that addition of 80 mM KCl in the organ bath induced contractions of the detrusor muscle strips. The addition of VFX (10^{-4}, 5×10^{-4} and 10^{-3} M) significantly reduced the maximum contractile response to KCl compared to the control by 42±12.5% (p<0.01), 87±3.06% (p<0.001) and 94.3±1.69% (p<0.001), respectively (n = 7) (Fig. 2, 4).

Effect of venlafaxine on ACh induced contractions: Acetylcholine (ACh) cumulatively (10^{-6}-10^{-3} M) produced dose-dependent contractions of detrusor muscle strips in

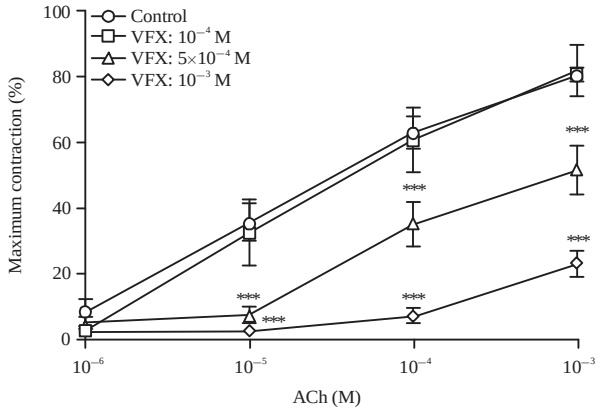

Fig. 5: Effect of VFX on the contractile responses of rat detrusor muscle to ACh

***p<0.001 compared to control group. Each point represents mean of 7 animals. Error bars show SEM

the control group. Treatment with VFX at doses of 10^{-4} M did not alter ACh-induced contractions, while administering 5×10^{-4} M or 10^{-3} M VFX reduced ACh-induced contractions. In the presence of 10^{-3} M ACh, the percent inhibition of contraction at these concentrations were 36.04±8.71% (p<0.001) and 71.64±4.44% (p<0.001), respectively (n = 7) (Fig. 2, 5).

Effect of venlafaxine and diltiazem on ACh induced contractions: To investigate the effect of VFX on calcium release from intracellular stores, responses to ACh were obtained in the presence of the calcium channel blocker diltiazem (10^{-4} M). It was determined that this dosage also blocks KCl-induced contractions (data not shown). The administration of 5×10^{-4} M VFX in combination with 10^{-4} M diltiazem did not change the contractile responses induced by ACh (10^{-6}-10^{-3} M), compared to diltiazem alone. In the presence of 10^{-3} M ACh, the percent inhibition of contraction induced by diltiazem alone was 76.16±2.80% and by VFX combined with diltiazem was 74.10±4.05% (p<0.001) (Fig. 6).

DISCUSSION

In the present study, it was demonstrated that venlafaxine (VFX) reduces Electrical Field Stimulation (EFS) as well as potassium chloride (KCl) and acethylcholine (ACh)-induced detrusor smooth muscle contractions in rats. Propranolol, a nonselective β-adrenergic receptor blocker, phentolamine, a nonselective α-adrenergic receptor blocker, methysergide, a nonselective serotonergic receptor blocker and naloxone, a non-selective opioid receptor blocker, did not

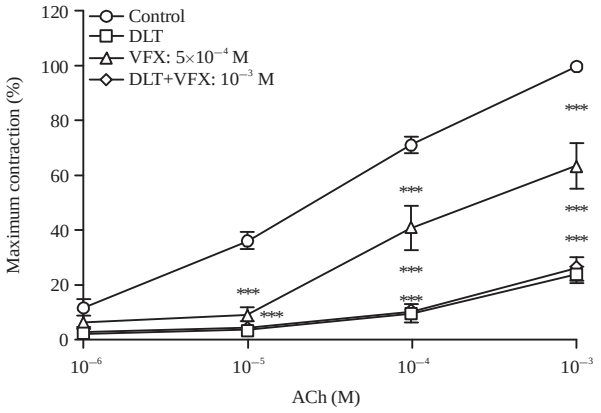

Fig. 6: Effect of VFX in presence of diltiazem (DLT) on the contractile responses of rat detrusor muscle to ACh

***p<0.001 compared to control group. Each point represents mean of 7 animals. Error bars show SEM

change the inhibitory effect of VFX on EFS response. Furthermore, administration of VFX in combination with diltiazem, a calcium channel blocker, did not change ACh-induced contractile responses compared to diltiazem alone.

There is conflicting evidence describing the effect of antidepressant drugs on bladder function. There are many publications that suggest that antidepressant drugs can be utilized in the treatment of urinary incontinence[10-12]. Tricyclic antidepressants are often used for this purpose because they have anticholinergic properties. Desipramine, an active metabolite of imipramine, may also be used in treatment of overactive bladder[13]. In addition, duloxetin, an SNRI antidepressant, has been demonstrated with clinical efficacy in the treatment of stress urinary incontinence and overactive bladder[4]. However, another study showed that duloxetine treatment reduced bladder overactivity resulting from cerebral infarction in rats[14]. Previous animal study has shown that VFX might alter the contraction of the detrusor muscle and bladder capacity[15]. The SSRIs have been shown to facilitate urine storage by inhibiting the parasympathetic voiding pathway. Reboxetine, a noradrenaline reuptake inhibitor, activates the alpha-1 adrenoceptors of the internal urethral sphincter, which might explain why urinary retention has been reported in a small number of male patients treated with this drug[16]. Although some antidepressants are used to treat urinary incontinence, others can cause urinary incontinence[17]. One possible explanation for the incontinence associated with SSRIs may be their agonistic effects on the 5-HT_4 receptors. VFX has been reported to induce urinary incontinence, possibly caused by inhibition of norepinephrine reuptake, with a consequent rise in the extracellular concentration of the drug through activation of multiple adrenergic receptor subtypes[18]. However, in another study, it was demonstrated that VFX had anticholinergic effects, which resulted in urinary retention[19].

In this study, the inhibitory effect of VFX on EFS-induced contractions was concentration dependent, with no significant effect at 10^{-4} M VFX (not including 32 and 64 Hz). There was significant inhibition at 5×10^{-4} M and 10^{-3} M VFX at all EFS ranges (2-64 Hz) on detrusor smooth muscle contraction. There are only a few studies that have investigated the effect of VFX on smooth muscles. In one study, which examined the effect of VFX on vascular smooth muscles, it was demonstrated that VFX did not relax aortal rings[20]. In another study, Bae *et al.*[21] showed that pretreatment with VFX (10^{-4} M) increased the contraction of detrusor strips following electrical stimuli at 8, 16 and 32 Hz. EFS-induced detrusor contractile response is mainly of neurogenic origin, as electrical stimulus acts on postganglionic nerves within the tissue, causing ACh release. In this study, reducing EFS responses with VFX suggests that this effect may be related to receptor or post-receptor events.

This inhibitory effect of VFX on rat detrusor muscle may be due to relaxation of the bladder smooth muscle. Many receptor systems play a role in bladder relaxation. Adrenoreceptors, particularly beta receptors and alpha-2 receptors, mediate bladder relaxation[22]. Moreover, serotonin receptors, especially 5-HT_7 and 5-HT_3 and opioidergic receptors, particularly the μ receptors, have also been demonstrated to mediate bladder relaxation[23, 24].

In this study, it was demonstrated that alpha and beta adrenergic, opioidergic and serotonergic receptor antagonists did not alter the inhibitory effect of VFX (5×10^{-4} M) on EFS-induced contractions of rat detrusor muscles. In a previous study, VFX increased the response of rat vas deferens to noradrenaline but did not alter the response of isolated rat uterus to serotonin[25]. In another study, it was shown that the inhibitory effect of St. John's wort, an herbal antidepressant, on EFS-induced contractions was unaffected by administration of phentolamine plus propranolol (an adrenergic blocker), haloperidol (a dopaminergic blocker), methysergide (a serotonergic blocker), capsazepine (which blocks the vanilloid receptor) or cannabinoid CB_1 receptor antagonist SR141716A[26]. In this study, it was demonstrated that adrenergic, opioidergic and serotonergic systems do not play a role in the inhibitory effect of VFX. The inhibitory effect of VFX on EFS-induced detrusor smooth muscle contractions may be associated with calcium release. Thus, possible role of intracellular and/or extracellular calcium in VFX-induced detrusor muscle relaxation was investigated.

Venlafaxine (10^{-4}-10^{-3} M) inhibited KCl-induced detrusor contractions. Depolarization of bladder muscle strips by high K^+ (80 mM) elicited contraction on detrusor muscle. Muscle stimulation by KCl treatment results in depolarization of the sarcolemma and activation of L-type calcium channels, which results in calcium entry from the extracellular space and consequently, contraction[27]. Previous study investigated the effect of antidepressants on K^+-induced smooth muscle contractions imipramine, mianserin and sertraline inhibited K^+- induced contractions in rat aortic rings[28]. It was suggested that this effect is due to the inhibitory effect of sertraline and mianserine on L-type calcium channels. The findings from this study support the idea that the VFX-induced inhibitory effect on muscle contraction depends critically on the reduced influx of Ca^{2+} from the extracellular space through L-type calcium channels.

Venlafaxine (5×10^{-4} and 10^{-3} M) also inhibited ACh-induced detrusor muscle contractions. The VFX in combination with 10^{-4} M diltiazem, a calcium channel blocker, did not change the contractile responses induced by ACh (10^{-6}-10^{-3} M) compared to diltiazem alone. The fact that VFX does not cause a further increase in the relaxant effect of diltiazem suggests that intracellular calcium has no role in the inhibitory effect of VFX on smooth muscle contraction.

A previous study investigating the effect of antidepressant drugs on ACh-induced detrusor contractions suggested that tricyclic antidepressants (imipramine, amitriptyline, trimipramine, clomipramine, nortriptyline and amoxapine)[7] reduce ACh response due to their anticholinergic properties. Current results suggest that the inhibitory effect of VFX on smooth muscle contractions may be due to a different mechanism of action. This effect is probably the result of a calcium channel blockage instead of antidepressant action. There are many studies that demonstrate the relationship between antidepressants and calcium channel regulation[29]. Antkiewicz-Michaluk[30] found that tricyclic antidepressants are linked to L-type calcium channels. They also suggest an interaction between tricyclic antidepressants and voltage-dependent calcium channels. Imipramine has been reported to suppress the L- type voltage-dependent calcium current in dorsal root ganglion cells[31]. Zahradnik *et al.*[32] suggested that antidepressants exert their inhibitory action on cardiac L-type calcium channels through a specific interaction at a receptor site in rat ventricular myocytes. Citalopram and amitriptyline exhibited concentration-dependent inhibition of the L-type calcium channel current in cardiomyocites[33]. Fluoxetine is an antidepressant that potently inhibits L-type Ca^{2+} in rat ventricular myocytes[34]. Using a whole-cell configuration of the patch clamp technique, a study also revealed that VFX blocks calcium channels on isolated guinea pig cardiac myocytes[35]. In this study, it was demonstrated that inhibition of the contractile response of rat detrusor muscle by VFX depended solely on the inhibition of extracellular calcium.

CONCLUSION

Venlafaxine has a clear inhibitory effect on the contraction of detrusor smooth muscles. In this study, it was demonstrated that VFX has no effect on noradrenergic, opioidergic and serotonergic receptors but does inhibit extracellular calcium entry through voltage-dependent calcium channels. Although VFX itself is not currently used as a treatment for urinary incontinence, further studies are required to develop VFX as a novel medical treatment for urinary incontinence.

SIGNIFICANCE STATEMENT

The clarification of the effects of antidepressant drugs on detrusor muscle function will help to understand the relationship between antidepressant usage and urinary incontinence which is a common health problem. The effect of venlafaxine, which is one of the most used antidepressant, on detrusor muscle functions needs to be elucidated. This *in vitro* study shows novelty by suggesting that venlafaxine has an inhibitory effect on detrusor muscle contraction and the underlying mechanism involves the inhibition of calcium entry to the cell.

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