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Do the anti-reproductive effects of fluoxetine involve changes in seminal vesicle contraction? A preclinical study

Os efeitos anti-reprodutivos da fluoxetina envolvem alterações na contração da vesícula seminal? Um estudo pré-clinico

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RESUMO

O tratamento com fluoxetina é capaz de induzir ejaculação retardada em humanos. Esse efeito pode ser o resultado da ação direta da fluoxetina no músculo liso da vesícula seminal, reduzindo sua atividade motora e a emissão do sêmen durante a ejaculação. Portanto, este estudo teve como objetivo avaliar os efeitos *in vitro* da fluoxetina nas contrações da vesícula seminal de ratos induzidas por KCl ou pelos agonistas autonômicos noradrenalina ou carbacol. A vesícula seminal de ratos foi isolada e montada em um sistema de banho de órgãos. Os tecidos foram submetidos a curvas de concentração-resposta para KCl, noradrenalina ou carbacol na ausência ou presença de fluoxetina (1, 3 ou 10 µM) pré-incubada por 40 minutos. Curvas concentração-resposta para KCl na presença de 3 µM de fluoxetina também foram geradas usando uma solução nutritiva normal, seguida pela adição cumulativa de $CaCl_2$, ou usando uma solução nutritiva com alta concentração de $CaCl_2$. A fluoxetina *in vitro* reduziu o efeito máximo do KCl, da noradrenalina e do carbacol na vesícula seminal de ratos. Os efeitos da fluoxetina nas contrações da vesícula seminal induzidas por KCl foram revertidos pela adição de cálcio exógeno ou atenuados quando os tecidos foram expostos a uma solução nutritiva contendo alta concentração desse íon. Em conclusão, a fluoxetina afeta negativamente a contratilidade da vesícula seminal de ratos.

Palavras-chave: Fluoxetina; Vesícula seminal; Ratos; Músculo liso; Atividade motora.

ABSTRACT

Fluoxetine treatment has been found to induce delayed ejaculation in humans. This effect may result from fluoxetine's direct action on the smooth muscle of the seminal vesicle, potentially hindering its motor activity and seminal emission during ejaculation. Therefore, this study aimed to assess the effects of *in vitro* fluoxetine on contractions of rat seminal vesicle induced by KCl or autonomic agonists noradrenaline or carbachol. The rat seminal vesicle was isolated and mounted in an organ bath setup. The tissues were subjected to concentration-response curves for KCl, noradrenaline, or carbachol in the absence or presence of fluoxetine (1, 3, or 10 µM) pre-incubated for 40 minutes. Concentration-response curves for KCl in the presence of 3 µM fluoxetine were also generated using a normal nutrient solution, followed by the cumulative addition of $CaCl_2$, or using a nutrient solution with a high concentration of $CaCl_2$. *In vitro* fluoxetine reduced the maximal effect of KCl, noradrenaline

and carbachol on rat seminal vesicle. The effects of fluoxetine on KCl-induced seminal vesicle contractions were reversed by adding exogenous calcium or attenuated when the tissues were bathed with nutrient solution containing a high concentration of this ion. In conclusion, fluoxetine negatively affects the contractility of rat seminal vesicle.

Keywords: Fluoxetine; Seminal vesicle; Rats; Smooth muscle; Motor activity.

INTRODUCTION

Fluoxetine is a selective 5-hydroxytryptamine (serotonin, 5-HT) reuptake inhibitor (SSRI) used for the long-term treatment of depression with well-known negative effects on male fertility. In addition, this drug is also indicated for the treatment of premature ejaculation, increasing the number of reproductive age men on SSRI therapy (PRATT et al., 2017; ROOSTAEE et al., 2025).

Studies performed in human or rodents have revealed that fluoxetine treatment exerts anti-reproductive effects, characterized by impairments in both sexual function (reduced libido, erectile dysfunction and delayed ejaculation) and semen quality (reduced number of sperm cells in ejaculate, decreased sperm motility, increased DNA fragmentation) (CHEN et al., 2025; DROBNIS, NANGIA, 2017). The exact mechanism underlying fluoxetine induced adverse effects on male reproduction remains under investigation. However, it appears to involve multiple mechanisms, including alterations in 5-HT levels in brain areas associated to orgasm and ejaculatory control, disruption of hypothalamic–pituitary–gonad axis, and impaired spermatogenesis. Additionally, it has been suggested that that fluoxetine may directly affect the contractility of smooth muscle in the genitourinary tract, such as in the vas deferens or epididymal duct, which could contribute to delayed ejaculation (BEZERRA et al., 2019; PEDROSO et al., 2017). Nevertheless, the effects of fluoxetine on the contractility of seminal vesicle smooth muscle, a key organ involved in ejaculation, have not yet been thoroughly investigated and warrant further research.

The seminal vesicles are paired glandular structures that play a crucial role in the male reproductive system. These organs consist of secretory glandular tissue, regulated by parasympathetic innervation, and smooth muscle, which is influenced by both the sympathetic and parasympathetic nervous systems. During the emission phase of ejaculation, sympathetic fibers from the hypogastric nerves stimulate contractions of the seminal vesicles and the prostate gland. This coordinated muscular activity facilitates the expulsion of spermatozoa and seminal fluid into the posterior urethra, enabling ejaculation (McKAY et al., 2023). It has also been reported that fluoxetine can induce significant histological alterations in rat seminal vesicles, primarily characterized by epithelial metaplasia, mucosal changes, and modifications in smooth muscle thickness. These alterations are suggested to potentially contribute to the delayed ejaculation associated with the use of this drug (AGGARWAL et al., 2014). However, the contractile function of the seminal vesicles was not evaluated in this study and may represent an additional mechanism by which fluoxetine affects ejaculation and, consequently, male reproductive capacity.

Therefore, this study aimed to evaluate the effects of *in vitro* fluoxetine on contractions of rat seminal vesicle induced by the depolarizing agent potassium chloride (KCl) or autonomic drugs such as noradrenaline (adrenoceptors agonist) or carbachol (muscarinic acetylcholine receptors agonist). Additionally, we sought to investigate the role of calcium, a key mediator of smooth muscle contraction, in the effects of fluoxetine on seminal vesicle contractility.

METHODS

Animals

Male (60–90 days old/200–300 g) Wistar rats were obtained from the Animal Facility of the Bioscience Center of the Federal University of Rio Grande do Norte (Natal, Brazil), and maintained under controlled conditions (25 °C, 12/12 h light/dark cycle) until the time of experiments. All experimental procedures described in this study were previously approved by the local Ethics Committee for the Use of Experimental Animals at the Federal University of Rio Grande do Norte (Protocol number 0058/2018) and are in accordance with the ARRIVE guidelines (KILKENNY et al., 2010).

Rat seminal vesicle isolation for organ bath studies

The animals were euthanized by decapitation. The seminal vesicles were exposed and carefully excised, cleaned from adjacent tissues (including copulatory plugs) and mounted in a 10 ml organ bath under 1.0 g tension. Tissues were bathed in a physiological salt solution (nutrient solution) with the following composition (mM): 138.0 NaCl; 5.7 KCl; 1.8 $CaCl_2$; 15.0 $NaHCO_3$; 0.36 $NaH_2PO_4 \cdot H_2O$, and 5.5 glucose, prepared in glass distilled deionized water, bubbled with air, and maintained at 32 °C and pH 7.4. Changes in isometric tension in the rat seminal vesicle were recorded with a force displacement transducer (Ugo Basile, Italy) coupled to a Gemini two-channel physiographic recorder (Ugo Basile, Italy). After a 30 min stabilization period, the tissues were incubated with KCl 80 mM for 5 min to evaluate tissue viability. The preparation was then washed out and after 40 min the experiments were performed.

Cumulative concentration-response curves for KCl or agonists in the absence or presence of fluoxetine in rat seminal vesicle

Cumulative concentration-response curves for KCl (depolarizing agent; 5, 10, 20, 40, 80 and 120 mM), noradrenaline (adrenoceptor agonist; 10^{-8}M – 10^{-4}M) or carbachol (muscarinic acetylcholine receptor agonist; 10^{-7}M – 10^{-3}M) were constructed in the absence or presence of three concentrations of fluoxetine (1, 3 and 10 µM). After checking tissue viability and equilibration time, isolated rat seminal vesicle was repeatedly stimulated with cumulative concentration-response curves for KCl, noradrenaline or carbachol (40 min between curves) until steady effects were obtained (usually two times). Thereafter, the curves to KCl, noradrenaline or carbachol were obtained in the absence (control) or presence of increasing concentrations of fluoxetine. Each concentration of antagonist was equilibrated with the tissues for 40 min and during intervals of successive curves the preparation was carefully washed out with nutrient solution.

In another set of experiments, cumulative concentration-response curves for KCl were constructed in the absence or presence of fluoxetine 3 µM. When maximum contractile effect of KCl in the presence of fluoxetine 3 µM was reached, cumulative concentration response curves for calcium chloride ($CaCl_2$; 3, 10, 30 and 100 mM) were immediately made without washing out the preparation. Thus, cumulative concentration-response curves for KCl were also constructed in the absence or presence of fluoxetine 3 µM in tissues bathed with nutrient solution containing $CaCl_2$ 10 mM.

Pharmacological parameters

The pharmacological parameters E_{max} (maximum contractile effect induced by an exogenous substance) and pEC_{50} (indicating potency, measured as the negative log of agonist concentration able to induce 50% of maximum response), were determined from cumulative concentration-response curves to allow comparisons between KCl/agonists curves in the presence or absence of fluoxetine.

Data and statistical analysis

The data were calculated as gram of contraction

(contraction g). Curve fitting by non-linear regression for the calculation of pEC_{50} and E_{max} was performed with Prism v.5 software (San Diego, CA, USA). Whenever appropriate, values are presented as means ± SEM. Non-paired t-tests were used for the comparisons between two groups. One-way ANOVA followed by the Dunnett's posttest was used for the comparisons of three or more groups. .Two-way ANOVA followed by the Bonferroni's posttest was used for comparisons between two categorical independent variables. A p value of less than 0.05 was considered to be statistically significant. The results were obtained from groups of at least five experiments with different tissues from distinct animals.

RESULTS

In vitro incubation of fluoxetine 1 µM, 3 µM and 10 µM were able to diminish the KCl-induced seminal vesicle contractions, as demonstrated by a significant reduction in the maximum effect of this depolarizing agent of 30%, 65% and 85%, respectively (Figure 1A, Table 1). The potency of KCl to promote seminal vesicle contractions was unaffected by fluoxetine incubation (Figure 1A; Table 1). Thus, only fluoxetine 10 µM was able to significantly decrease the maximum contractile effects of noradrenaline or carbachol in seminal vesicle by about 70% and 60%, respectively, without altering the potency of these agonists (Figure 1A and 1B; Table 1).

Table 1: Maximal contractions (Emax) and the negative log of agonist concentration able to induce 50% of maximum response (pEC50) values for potassium chloride (KCl), noradrenaline or carbachol in the absence (control) or presence of fluoxetine (1, 3 or 10 µM; pre-incubated for 40 min) in isolated seminal vesicle of rats.

	Pharmacological Parameters	
KCl	**E_{max}**	**pEC_{50}**
Control (n=6)	2.1 ± 0.20	1.7 ± 0.04
+ fluoxetine 1 µM (n=6)	1.5 ± 0.22[a]	1.6 ± 0.02
+ fluoxetine 3 µM (n=6)	0.7 ± 0.09[a]	1.6 ± 0.02
+ fluoxetine 10 µM (n=6)	0.3 ± 0.04[a]	1.7 ± 0.03
Noradrenaline	**E_{max}**	**pEC_{50}**
Control (n=6)	1.7 ± 0.22	6.6 ± 0.06
+ fluoxetine 1 µM (n=6)	1.4 ± 0.16	6.7 ± 0.05
+ fluoxetine 3 µM (n=6)	1.1 ± 0.17	6.8 ± 0.06
+ fluoxetine 10 µM (n=6)	0.5 ± 0.08[a]	6.6 ± 0.06
Carbachol	**E_{max}**	**pEC_{50}**
Control (n=5)	1.2 ± 0.11	4.8 ± 0.06
+ fluoxetine 1 µM (n=5)	1.16 ± 0.16	4.6 ± 0.08
+ fluoxetine 3 µM (n=5)	0.9 ± 0.11	4.7 ± 0.09
+ fluoxetine 10 µM (n=5)	0.5 ± 0.08[a]	4.6 ± 0.08

Values are Means ± S.E.M. n, sample size.
[a] P<0.05 in relation to control.

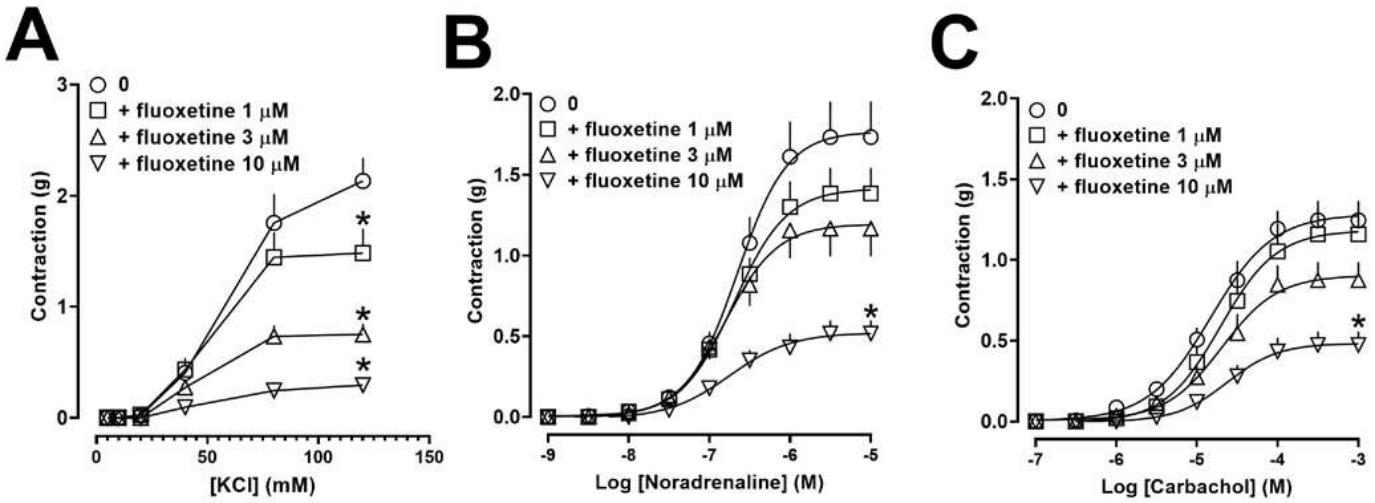

Figure 1 – Effects of *in vitro* fluoxetine on contractions of rat seminal vesicle induced by KCl, noradrenaline or carbachol. Contractions obtained from cumulative concentration-response curves for potassium chloride (KCl) (panel A; n=6), noradrenaline (panel B; n=6) or carbachol (panel C; n=5) in the absence (control) or presence of fluoxetine 1, 3 or 10 μM pre-incubated for 40 min. Each point represents Means ± S.E.M. of at least 5 independent experiments performed with tissues from different animals. *P < 0.05 in relation to E_{max} of control. ANOVA one-way followed by the Dunnett's posttest

The cumulative addition of $CaCl_2$ reversed the suppression of the maximum contractile effect of KCl promoted by fluoxetine 3 μM (Figure 2A). The maximum contractile effect of KCl were also decreased by fluoxetine 3 μM in seminal vesicles bathed with nutrient solution containing Ca^{2+} 10 mM (Figure 2B). However, the effects of fluoxetine 3 μM on KCl induced seminal vesicle contractions were of lesser extent in nutrient solution containing Ca^{2+} 10 mM (KCl E_{max} reduction of 30%) compared to normal nutrient solution (containing Ca^{2+} 1.8 mM) (KCl E_{max} reduction of 60%) (Figure 2C).

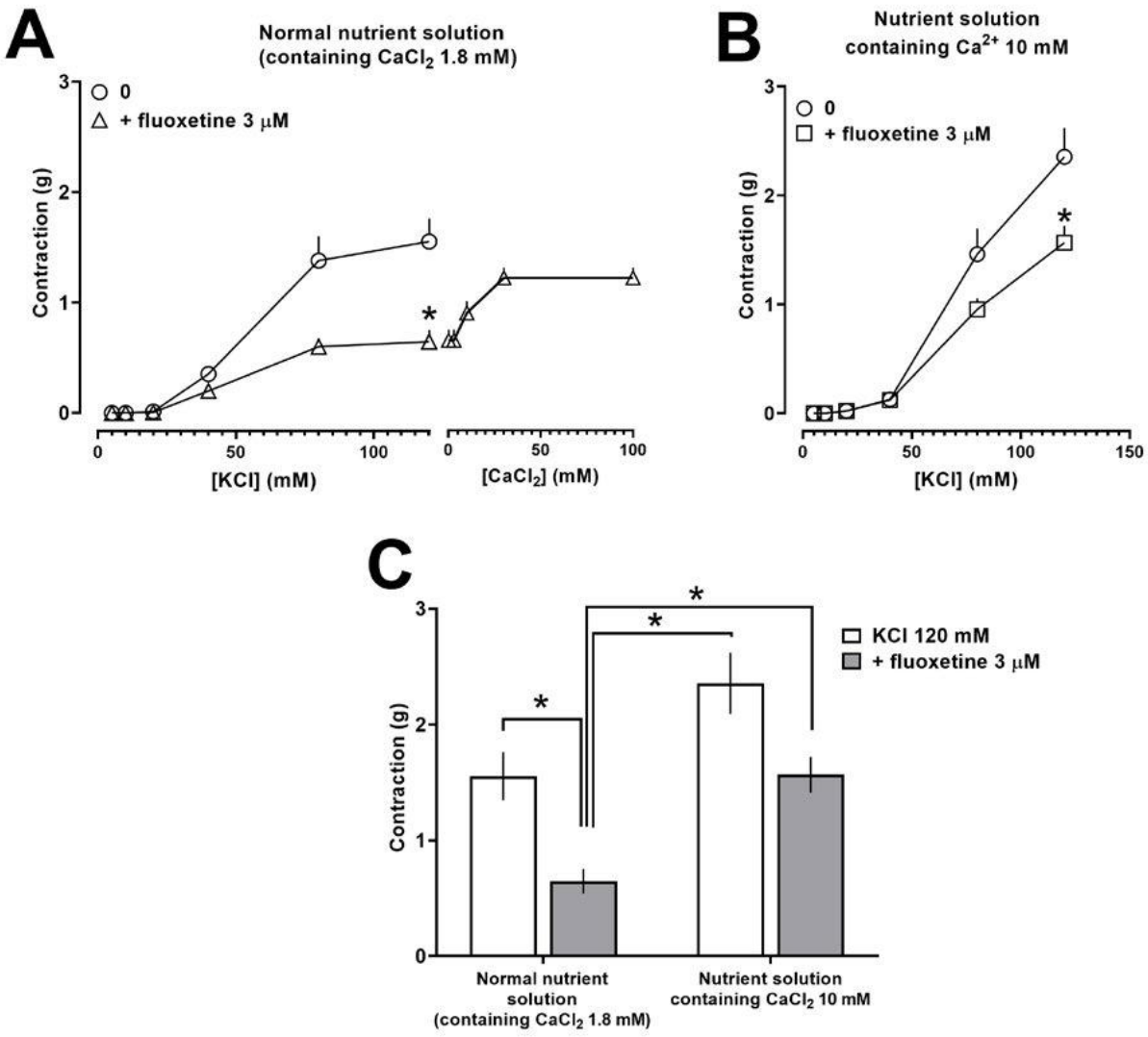

Figure 2 – Effects of *in vitro* fluoxetine on potassium chloride (KCl)-induced rat seminal vesicle contraction in normal nutrient solution or nutrient solution containing high Ca^{2+} concentration . Contractions obtained from cumulative concentration-response curves for KCl in the absence (control) or presence of fluoxetine 3 µM pre-incubated for 40 min in normal nutrient solution followed by cumulative addition of calcium chloride ($CaCl_2$) (panel A; n=5) in nutrient solution containing high Ca^{2+} concentration ($CaCl_2$ 10 mM) (panel B; n=6). Each point represents Means ± S.E.M. of at least 5 independent experiments performed with tissues from different animals. *P < 0.05 in relation to E_{max} of control. Unpaired Student t Test. Panel C shows a bar graph comparing the effect of fluoxetine 3 µM pre-incubated for 40 min on seminal vesicle contractions induced by KCl 120 mM in nutrient solution containing high Ca^{2+} concentration ($CaCl_2$ 10 mM). Each bar represents Means ± S.E.M. extracted from panel A and B. *P < 0.05 between groups indicated by zig zag lines.

DISCUSSION

In this study, we found that *in vitro* fluoxetine reduced the contractile responses of the rat seminal vesicle promoted by KCl or by adrenergic or cholinergic agonists. Furthermore, we showed that the effects of fluoxetine on KCl-induced seminal vesicle contractions were reversed by adding exogenous calcium or attenuated in tissues bathed with nutrient solution containing a high concentration of this ion.

The seminal vesicle is a secretomotor organ considered fundamental for male fertility. This organ is responsible for producing the seminal fluid which contains several substances that ensure semen function, sperm survival and correct fertilization. After its production, the seminal fluid is released into the ejaculatory duct, and then into the prostatic urethra, by the motor activity of seminal vesicle smooth muscle. The seminal vesicle smooth muscle contraction is mediated by both noradrenaline (via α_1-adrenoceptors) and acetylcholine (via M_3 receptors) released from nerve endings of sympathetic and parasympathetic nervous system, respectively (KIGUTI, PUPO, 2012; HAMAMURA et al., 2006; McKAY et al., 2023). In addition, it is described that the contractions of seminal vesicle evoked by adrenergic/cholinergic agonists or by depolarizing agent KCl are dependent on Ca^{2+} influx through voltage dependent calcium channels (KIGUTI, PUPO, 2012; HAMAMURA et al., 2006; SHARIF, 1993).

Several studies have demonstrated that fluoxetine > 3 µM decreases smooth muscle contraction induced by KCl, adrenergic (noradrenaline or phenylephrine) or cholinergic agonists (carbachol) in rat genitourinary tissues such as vas deferens or epididymal duct (BEZERRA et al., 2019; PEDROSO et al., 2017). In this context, we hypothesized that fluoxetine could also affect rat seminal vesicle contractions. Indeed, we demonstrated that *in vitro* fluoxetine produced inhibitory effects on rat seminal vesicle contractions, regardless of the pharmacological stimuli employed (KCl, noradrenaline, or carbachol). This suggests that fluoxetine may interfere with a common component of the signaling pathway triggered by receptor activation or depolarizing stimuli.

The inhibitory effects of fluoxetine on smooth muscle contractions induced by different pharmacological stimuli are usually attributed to the blockade of voltage dependent calcium channels, leading to a decrease in the Ca^{2+} influx after receptor activation or KCl-mediated depolarization, as previous described by several studies (BUSCH et al., 2000; PEDROSO et al., 2017; UNGVARI et al., 2000; UNO et al., 2017). In our study, we found that the effects of fluoxetine 3 µM on KCl-induced seminal vesicle contractions were diminished by adding $CaCl_2$ to the preparation, indicating that Ca^{2+} signaling could be involved in the fluoxetine effects on the rat seminal vesicle contractility. However, more studies are necessary to confirm the participation of calcium channels in the effects of fluoxetine on rat seminal vesicle contractility.

Although the fluoxetine-induced decrease in seminal vesicle contractility may explain the impairment of the ejaculation in patients treated with this antidepressant, other peripheral mechanisms may also be involved. For example, fluoxetine treatment is able to reduce serum testosterone levels in rodents (BEZERRA et al., 2019; ERDEMIR et al., 2014) and cell lines (HANSEN et al., 2017). Seminal vesicle contraction is also an androgen-dependent process (ABREU et al., 1980; McKAY et al., 2023). Therefore, fluoxetine induced alterations on seminal vesicle function could be also a consequence of an anti-androgenic activity of this drug. Studies evaluating the *in vivo* effects of long-term treatment with fluoxetine on the secretomotor activity of the seminal vesicle are necessary to understand the effects of this drug on seminal vesicle function and its consequence on male fertility.

It is noteworthy to mention that although alterations in seminal vesicle contractility may significantly impact

male reproductive capacity, the evidence remains limited (GAO et al., 2024). For example, Kiguti and Pupo (2012) demonstrated that tamsulosin (α_{1A}-adrenoceptor antagonist), nifedipine and (S)-(+)-niguldipine (L-type calcium channel blockers) reduced rat seminal vesicle contractility induced by noradrenaline. However, no changes in ejaculatory latency were observed in rats treated with these drugs, although tamsulosin decreased the number and weight of seminal plugs recovered from female rats. In summary, while seminal vesicle contractility is crucial for normal ejaculation, its specific role in male sexual dysfunctions remains unclear. More studies are needed to elucidate how alterations in seminal vesicle function might contribute to ejaculatory disorders.

CONCLUSION

In conclusion, *in vitro* fluoxetine negatively affects rat seminal vesicle contractions induced by KCl, adrenergic, or cholinergic agonists, likely through disruption of Ca^{2+}-dependent signaling pathways that are fundamental to smooth muscle contractility. Further research is required to clarify the mechanisms of fluoxetine's effects on seminal vesicle function and to determine how these effects translate to clinical outcomes, such as ejaculatory disorders and overall male reproductive capacity.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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