



## The Influence of Atypical Antipsychotic Drugs on Vas Deferens in Mice

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### ABSTRACT

**Objective:** Several classes of prescription drugs contribute to the sexual dysfunction in men that have been found especially in the antipsychotic drugs. Varieties of mechanisms are likely to contribute to the antipsychotic-related sexual dysfunction including hyperprolactinemia and antagonism of some neurotransmitter receptors. Implications for future research, atypical antipsychotics should be strongly taken into account. **Material and Method:** Male mice were treated by intraperitoneal injection (IP injection) of drugs for 21 days. The effects of saline, quetiapine, olanzapine, and risperidone were investigated on serotonin, noradrenaline (NA), adenosine triphosphate (ATP) and potassium chloride (KCl) which induced contractions of the vas deferens. **Results:** Serotonin-induced contractile responses were significantly increased in the epididymal and prostatic portion of the vas deferens obtained from the risperidone-treated group. The  $E_{max}$  value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from the risperidone-treated group than the control group. However, olanzapine and quetiapine treatment had no effect on serotonin responses in both epididymal and prostatic portions of the mice vas deferens. The risperidone treatment significantly inhibited both noradrenaline and ATP-induced contractions of the prostatic and epididymal portions of the mice vas deferens. There were no significant differences in KCl-induced contractile responses among the groups. **Conclusion:** It can be concluded that only risperidone could impair sexual competence in the male mice. Serotonergic, noradrenergic and purinergic receptors may contribute to the changes in vas deferens contractions in mice with chronic treatment of risperidone but not olanzapine and quetiapine. This study will help clinicians make a purpose-oriented choice of which antipsychotic drug to use.

**Keywords:** Antipsychotic drugs, Risperidone, Olanzapine, Quetiapine, Sexual dysfunction

### INTRODUCTION

Psychotropic medications are prescribed to treat a variety of psychiatric disorders such as depression, anxiety, and psychosis. However, these drugs have various side effects, including sexual dysfunction [1]. Sexual dysfunction related to the psychotropic medications is the major problem in patients taking antipsychotics drugs. This situation affects the quality of life and the treatment compliance, in the long term treatments [2]. Since sexual dysfunction may occur as a result of a psychiatric disorder or medication, assessment of sexual function is important in patients with psychiatric illness [3].

Hyperprolactinemia is one of the most common antipsychotic-induced adverse events in the psychiatric patients, especially patients treated with first-generation antipsychotics or the second generation antipsychotics risperidone or amisulpride [4-7]. In schizophrenia patients, the hyperprolactinemia rate was increased in patients treated with risperidone compared with quetiapine, olanzapine, clozapine, and aripiprazole [8-10]. As a result of an increase in plasma prolactin levels, amenorrhea and galactorrhea in women, gynecomastia and lactation in men, and sexual dysfunction in both genders were seen [9-12].

As known, dopamine plays a role in the neuroendocrine control of prolactin secretion from the anterior pituitary gland as an inhibiting factor. Again, antipsychotic drugs block dopaminergic receptors. Thus, blockade of pituitary

dopamine D2 receptors causes an increase in the prolactin secretion. Hyperprolactinemia inhibits gonadotropin-releasing hormone (GnRH) secretion from hypothalamus which is important for the emergence of sexual dysfunction. Apart from hyperprolactinemia, other mechanisms are likely to contribute to antipsychotic-related sexual dysfunction. Sedation and blockade of neurotransmitter receptor ( $\alpha$ -adrenergic, histaminic and muscarinic) are some of them [13-15].

Due to the difficulty of the clinical investigations on drugs affecting the ejaculation process, animal experiments have become important. In the present study, we aimed to investigate the chronic effects of quetiapine, olanzapine and risperidone on serotonin, noradrenaline, adenosine 5'-triphosphate (ATP), and KCl-induced contractions of the vas deferens in mice.

## MATERIALS AND METHODS

### Animals

Male inbred BALB/c ByJ mice (Animal Research Center, Bursa-Turkey) aged 7 weeks was used in this study. Animals (4-5 per cage) were kept in the laboratory at  $21 \pm 1.5^\circ\text{C}$  with 60% relative humidity under a 12 hour light/dark cycle (light on at 8.00 pm) for 2 weeks before experimentation. Tap water and food pellets were available *ad libitum*. All procedures involving animals were in the compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Number: 29.12.2014, Kocaeli, Turkey).

### Drugs

Quetiapine, olanzapine, risperidone, serotonin creatinine sulphate, noradrenaline bitartrate, and potassium chloride were purchased from Sigma Chemicals (St Louis, Mo, USA). All drugs were dissolved in 0.9% physiological saline. Saline was used as the vehicle controls. Quetiapine, olanzapine, and risperidone were given intraperitoneally (IP) in a volume of 0.1 ml/10 g body weight of the mice. All used doses were selected on the basis of the previous behavioural studies [16-18]. Drugs were prepared freshly on the day of the experiment.

### Experimental Design

The mice were randomly divided into experimental groups as follows: saline, quetiapine 5 mg/kg, quetiapine 10 mg/kg, olanzapine 1 mg/kg, olanzapine 2 mg/kg, risperidone 0.25 mg/kg, risperidone 0.5 mg/kg. Mice were treated by IP injection of drugs for 21 days. Mice receiving only the vehicle IP (0.9% saline) during 21 days were served as the control group. Each experimental group consisted of 7 mice.

After 21 days of treatment, all animals were sacrificed by decapitation, the abdomen was opened and the vas deferens from each side was quickly removed. The vas deferens was divided into prostatic and epididymal halves of 1-2 cm in length described by Ventura [19]. Epididymal and prostatic portions of vas deferens were surgically dissected free and immersed in 20 mL organ baths containing Krebs' solution containing (mM): 113 NaCl, 4.8 KCl, 2.5 CaCl<sub>2</sub>, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 1.2 MgSO<sub>4</sub>, 25 NaHCO<sub>3</sub>, and 11.7 C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> which was equilibrated with 95% O<sub>2</sub>/5% CO<sub>2</sub> at 37°C during the study. The tissues were connected to an isometric force transducer (FDT 10 A Commat Iletisim, Ankara, Turkey) for the measurement of isometric force, which was continuously recorded on a computer via a four-channel transducer data acquisition system (MP150 Biopac Systems Inc. Goleta) using software (ACQ4.0 Biopac Systems Inc. Goleta) that had the capacity to analyze the data. The upper end was connected to the transducer and the lower end was fixed. After mounting, each strip was allowed to equilibrate with a basal tension of 1 g for 1 hour, with the Krebs-Henseleit solution which was replaced after every 15 min with fresh solution. At the end of the equilibration, strips were depolarized with 80 mM KCl in Krebs solution and were allowed to equilibrate for 30 min. After equilibration, the concentration-response curves to serotonin (10<sup>-8</sup> M to 10<sup>-4</sup> M), noradrenaline (10<sup>-8</sup> M to 10<sup>-4</sup> M), and ATP (10<sup>-8</sup> M to 10<sup>-4</sup> M) were obtained cumulatively. Each response was allowed to plateau before the addition of the next drug bolus. Following the completion of each drug concentration-response curve, tissues were washed for further 30 min.

### Analysis of Data

Results are expressed as the mean  $\pm$  SEM of different experiments. Contractile responses to serotonin, noradrenaline, and ATP were calculated as a percentage of the maximal contraction caused by KCl (80 mM). To evaluate the effects of agonists, maximum responses ( $E_{\text{max}}$ ) were calculated. Statistical comparison between the groups was performed using ANOVA supported by Dunnett's post-hoc test. Results were considered to be significantly different at  $p < 0.05$

RESULTS

Serotonin-induced contractions were significantly increased in both prostatic and epididymal portion of the mice vas deferens obtained from the risperidone (0.25 mg/kg and 0.5 mg/kg) groups. Figure 1 shows the epididymal data compared with the control group (p<0.05).

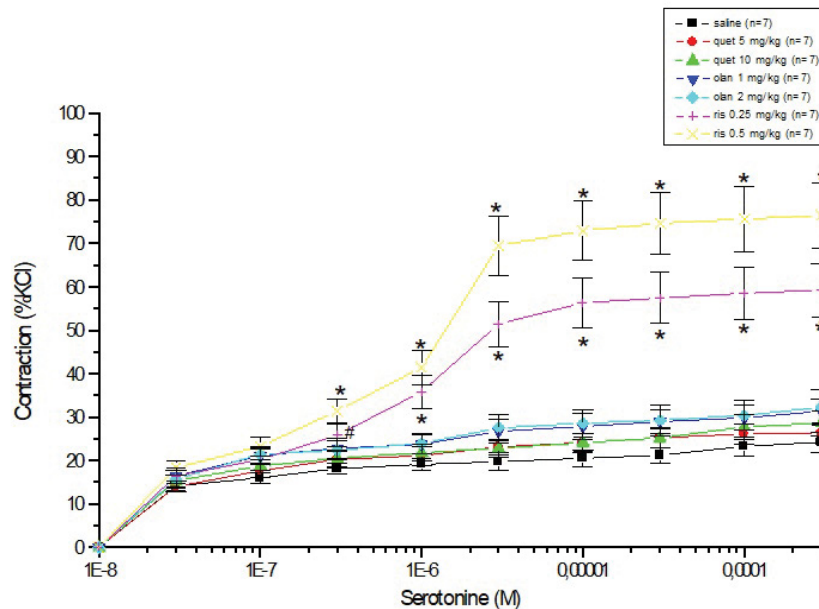


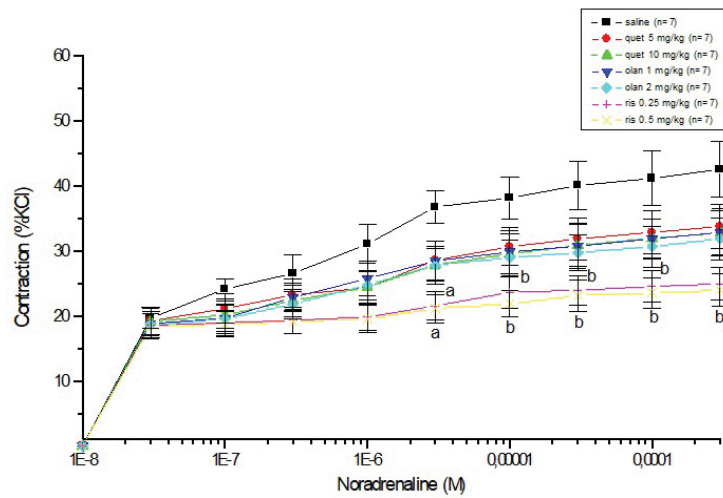
Figure 1 Serotonin concentration-responses curves in an isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). Number of mice in each group is shown in parenthesis

The E<sub>max</sub> value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from the risperidone-treated groups than in the control group (p<0.05) (Table 1). Quetiapine (5 mg/kg and 10 mg/kg) and olanzapine (1 mg/kg and 2 mg/kg) treatments had no effect on the serotonin-induced contractile responses in either portion of the vas deferens.

Table 1 E<sub>max</sub> (%) of 80 mM KCl values for serotonin, noradrenaline and ATP, and E<sub>max</sub> value (mg) for 80 mM KCl in vas deferens obtained from quetiapine, olanzapine and risperidone treatment and control mice (n=7)

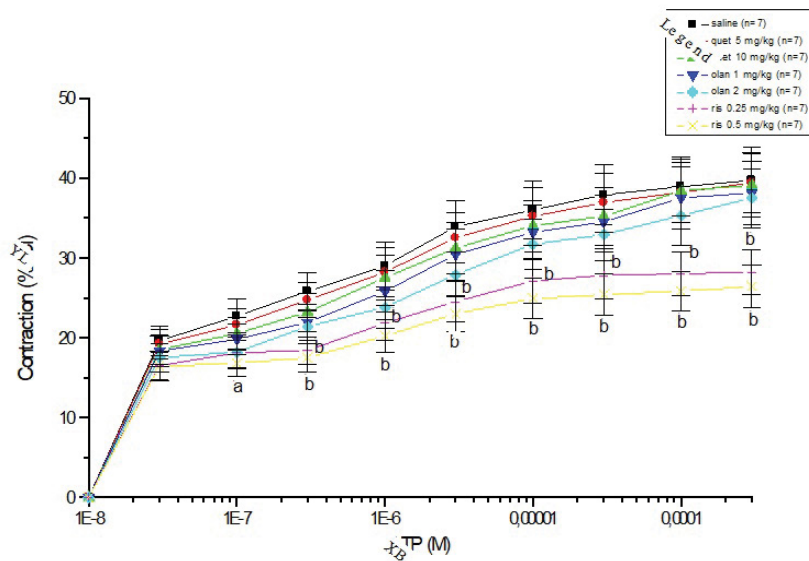
Variable	Control (mean ± SEM)	Quetiapine 5 (mean ± SEM)	Quetiapine 10 (mean ± SEM)	Olanzapine 1 (mean ± SEM)	Olanzapine 2 (mean ± SEM)	Risperidone 0.25 (mean ± SEM)	Risperidone 0.5 (mean ± SEM)
<b>Epididymal</b>							
KCl	1672 ± 208	1342 ± 173	1282 ± 161	1372 ± 191	1315 ± 213	1296 ± 226	1354 ± 194
Serotonin	24 ± 2	26 ± 2	29 ± 2	30 ± 3	30 ± 4	57 ± 4*	75 ± 6*
NA	43 ± 4	34 ± 3	33 ± 3	33 ± 4	32 ± 3	25 ± 3*	24 ± 3*
ATP	40 ± 4	39 ± 4	39 ± 4	38 ± 4	38 ± 4	28 ± 3*	26 ± 3*
<b>Prostatic</b>							
KCl	1844 ± 192	1876 ± 241	1902 ± 276	1812 ± 296	1798 ± 184	1862 ± 182	1804 ± 163
Serotonin	15 ± 2	16 ± 2	17 ± 2	17 ± 2	17 ± 2	32 ± 3*	37 ± 4*
NA	16 ± 1	15 ± 2	15 ± 2	14 ± 2	14 ± 2	7 ± 2*	6 ± 2*
ATP	25 ± 3	24 ± 2	23 ± 2	22 ± 2	21 ± 2	10 ± 2*	8 ± 1*

Risperidone treatment significantly inhibited noradrenaline-induced contractions in both the prostatic and epididymal portions of the mice vas deferens, epididymal data is shown in Figure 2 (p<0.05). The E<sub>max</sub> value for NA was significantly lower in risperidone-treated groups than in the control group (p<0.05) (Table 1). Quetiapine and olanzapine treatment had no effect on the NA-induced contractile responses in either portion of the vas deferens.



**Figure 2** Noradrenaline concentration-responses curves in an isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean  $\pm$  standard error of the mean (SEM). Number of mice in each group is shown in parenthesis

Risperidone treatment significantly inhibited ATP-induced contractions in both the prostatic and epididymal portions of the mice vas deferens, epididymal data is shown in Figure 3 ( $p < 0.05$ ). The  $E_{max}$  value for ATP was significantly lower in risperidone-treated groups than in the control group ( $p < 0.05$ ) (Table 1). Quetiapine and olanzapine treatment had no effect on the ATP-induced contractile responses in either portion of the vas deferens.



**Figure 3** ATP concentration-responses curves in an isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean  $\pm$  standard error of the mean (SEM). Number of mice in each group is shown in parenthesis

There were no significant differences in KCl-induced contractile responses among the groups (Table 1).

### DISCUSSION

Ejaculation is a natural part of the male sexual function. This coordinated muscular and neurological event can be divided into two distinct phases: emission and ejection [20]. In the regulation of ejaculation event, dopamine and serotonin are the essential neurotransmitters. Dopamine (via D2 receptors) promotes the ejaculation, but serotonin inhibits [21].

The present investigation aimed to reveal how vas deferens contractile functions are affected by using chronic

antipsychotic medication, and partially to clarify the mechanism of sexual dysfunction. Again, we believe that the results of this study will assist clinicians in their decision-making processes.

In a study, it was shown that the epididymal and prostatic parts of vas deferens are mainly innervated by the noradrenergic and purinergic system, and also epididymal and prostatic parts of vas deferens have different contraction characteristics [22]. Because of this, in the present study, we investigate the parts of vas deferens separately. We determined that serotonin-induced contractions are significantly increased in epididymal and prostatic parts of vas deferens obtained from risperidone-treated mice but not from quetiapine and olanzapine-treated mice. However, NA-induced and ATP-induced contractions are significantly reduced in both portions of the vas deferens obtained from the risperidone-treated mice but not from quetiapine and olanzapine-treated mice.

Sexual dysfunction is more common in antipsychotic users with increased prolactin levels was, but this was not seen with quetiapine and olanzapine users with no increase in prolactin levels. An elevated level of prolactin decreases serum testosterone secretion in men, thus, male sexual behaviors are impaired.

On the other hand, serotonin has an important role in the control of sexual behavior. High-levels of central serotonin is associated with the inhibition of ejaculation [23]. It was demonstrated that contractile responses to serotonin increased in the epididymal and prostatic portions of the vas deferens was obtained from fluoxetine-treated rats, rather than the control group [24]. It was shown that fluoxetine, sertraline, and paroxetine significantly increased ejaculation latency in patients with premature ejaculation and this is the evidence that serotonin plays an important role in delaying ejaculation [25].

A previous study showed that contractile responses of gastric fundus strips to the serotonin enhanced in haloperidol-treated rats. But, serotonin-evoked contractions decreased in fundus strips incubated with prolactin for 24 hours [26]. Based on these results, it can be said that prolactin modulates serotonergic activity indirectly, and enhances sensitivity to serotonin.

In the present study, we found that serotonin-induced contractions were significantly increased in both prostatic and epididymal portion of the mice vas deferens after risperidone treatment. Risperidone may increase the sensitivity to endogenous serotonin by receptor up-regulation or increase in post-receptor susceptibility. In contrast to risperidone group, there was no change found in the serotonin responses in mice treated with quetiapine and olanzapine, compared to control mice. This result may partly explain why it does not cause sexual dysfunction.

Sympathetic transmission is mainly mediated through noradrenaline and ATP, which is present in sympathetic nerves in the vas deferens of animals [27]. It is well known that adrenergic and purinergic mechanisms are necessary for the contraction of the vas deferens. However, in this study noradrenaline-induced and ATP-induced contractions were decreased in both portion of the vas deferens obtained from mice treated with risperidone, but not quetiapine or olanzapine. It may be said that inhibitions of noradrenergic and purinergic activities by risperidone contribute to the sexual dysfunction.

## CONCLUSION

This study shows that chronic treatment with risperidone affects vas deferens motility. Serotonergic, noradrenergic and purinergic receptors may, at least in part, contribute to changes in vas deferens contractions in mice with chronic treatment of risperidone but not quetiapine and olanzapine. These results may partly explain why risperidone but not quetiapine and olanzapine cause sexual dysfunction. We think that, in patients with sexual dysfunction, it is better to choose quetiapine and olanzapine than risperidone. Again, the results of this study will help psychiatrists to minimize the risk of sexual dysfunction in patients who need antipsychotic medication.

## DECLARATIONS

### Conflict of Interest

The authors have disclosed no conflict of interest, financial or otherwise.

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