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Loksapin, İloperidon, Paliperidon'un İzole Farelerde Vas Deferens Kasılması Üzerine Kronik Etkileri

Chronic Effects of Loxapine, Iloperidone, Paliperidone on Mice Isolated Vas Deferens Contractility

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ÖZ

Amaç: Erektil disfonksiyon, antipsikotiklerin olağan bir yan etkisidir; bu da hastaların ilaç kullanmaktan kaçınmasına neden olur. Bu çalışmanın amacı iloperidon, paliperidon ve loksapin'in farelerde serotonin (5-HT), noradrenalin (NA), adenozin trifosfat (ATP) ve potasyum klorür (KCl) ile indüklenen vas deferens kasılmaları üzerine etkilerini araştırmaktır.

Materyal ve Metot: Fareler rastgele deney gruplarına ayrıldı ve 21 gün boyunca ip enjeksiyonu ile tedavi edildi. Tedaviden sonra, ilaçların farelerin vas deferens şeritlerinin epididimal ve prostatik bölümlerinde 5-HT, ATP, NA ve KCl ile indüklenen kasılma tepkileri üzerindeki etkileri araştırıldı.

Bulgular: İloperidon, paliperidon ve loksapin ile tedavi edilen gruplardan elde edilen vas deferensin her iki bölümünde 5-HT ile indüklenen kasılma tepkileri önemli ölçüde artarken ATP ile indüklenen kasılma tepkileri önemli ölçüde azaldı. Bununla birlikte, bu ilaçların, fare vas deferens'in NA ve KCl ile indüklenen kasılmaları üzerinde önemli bir etkisi olmamıştır.

Sonuç: Bu sonuçlar, iloperidon, paliperidon ve loxapin'in kronik tedavilerinden serotonin ve ATP kaynaklı vas deferens kasılmalarının etkilendiğini göstermiştir. Bu ilaçlarla kronik olarak tedavi edilen farelerde, serotonerjik ve purinerjik reseptörler, erektil disfonksiyona neden olan vas deferens kasılmalarındaki değişikliklere katkıda bulunabilir.

Anahtar Kelimeler: Erektil disfonksiyon, iloperidon, in vitro, loksapin, paliperidon

ABSTRACT

Objective: Erectile dysfunction is a usual side effect of antipsychotic medications; this causes patients to avoid using drugs. The aim of this study to investigate the effects of iloperidone, paliperidone and loxapine on serotonin (5-HT), noradrenaline (NA), adenosine triphosphate (ATP) and potassium chloride (KCl)-induced contractions of the vas deferens in mice.

Materials and Methods: The mice were randomly divided into experimental groups and treated by ip injection of drugs for 21 days. After the treatment, the effects of drugs were investigated on 5-HT, ATP, NA and KCl-induced contractile responses in the epididymal and prostatic portions of mice vas deferens strips.

Results: 5-HT-induced contractile responses were significantly increased while ATP-induced contractile responses were significantly decreased in the both portions of the vas deferens obtained from the iloperidone, paliperidone and loxapine-treated groups. However, these drugs had no significant effect on NA- and KCl-induced contractions of mice vas deferens.

Conclusion: These results showed that serotonin and ATP -induced contractions of vas deferens were affected by the chronic treatments of iloperidone, paliperidone, and loxapine. In mice chronically treated with these drugs, serotonergic and purinergic receptors may contribute to changes in vas deferens contractions that cause erectile dysfunction.

Keywords: Erectile dysfunction, iloperidone, in vitro, loxapine, paliperidone

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INTRODUCTION

Sexual dysfunction is a significant public health problem of patients with schizophrenia.[1,2] Erectile dysfunction is the usual side effect of antipsychotic medications.[1,3,4] Moreover, sexual dysfunctions may diminish a person's quality of life and cause sexual problems.[5]

Inhibition of testosterone secretion due to high prolactin levels affects sexual function, which causes a reduction in sexual desire. On the other hand, hypothalamic dopamine has an inhibitory effect on prolactin release. Antipsychotic drugs that reduce dopaminergic activity lead to an increase in prolactin levels. Contrary to the suppressive effect of dopamine on prolactin, an increase in 5-HT activity causes prolactin release.[6,7]

Ejaculation is provided by both the autonomic and somatic nervous systems; it consists of two phases as emission and expulsion. The emission phase is generally under the control of sympathetic nervous system through noradrenaline (NA), ATP, NO, vasoactive intestinal peptide (VIP), and neuropeptide-Y neuromediators. On the other hand, the expulsion phase is under the influence of the autonomic and somatic nervous system through the NA, acetylcholine, ATP, NO, and VIP neurotransmitters.[8]

Iloperidone is a second-generation ''atypical'' antipsychotic. Its primary mechanism of action is combined D2/5HT2A antagonism.[9] Iloperidone has a high affinity for both D2 and 5HT2A receptors.[10]

Paliperidone or 9-hydroxy risperidone is the major active metabolite of risperidone. Paliperidone acts on dopamine D2 and serotonin 5HT2A receptors as an antagonist and also antagonizes the α1- and α2-adrenergic receptors and H1-histaminergic receptors.[11]

Loxapine is a post-synaptic antagonist at the D2 receptor and antagonist at the serotonin 5-HT2A, histaminergic H1, cholinergic M1, and adrenergic α1 receptors. Loxapine binds to the D4 receptor with higher affinity than to other dopaminergic receptors in human and animal models. [12] Also, loxapine has effects on Na-K and K-ATP channels, inhibits TREK1 and TREK2 of K channels.[13]

Sexual dysfunction is an important side effect of antipsychotic drugs; however, pharmacology studies about ejeculatory disorders is limited to clinical studies with registered drugs affecting the ejaculation process; therefore animal studies seems essential. According to these knowledge, the aim of this work was to investigate the effects of chronic iloperidone, paliperidone, and loxapine usage on serotonine, adenosine triphosphate (ATP), noradrenaline and KCl-induced contractions of the vas deferens in order to evaluate the effect of iloperidone, paliperidone and loxapine on the motility of the vas deferens in mice.

MATERIALS AND METHODS

Ethical Status: All procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Date: 22.07.2014, decision no: KOÜ HADYEK 7/4-2014).

Animals: Male inbred BALB/c ByJ mice (Animal Research Center, Bursa-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. Animals (4–5 per cage) were kept in the laboratory at 21 ± 1.5 ◦C with 60% relative humidity under a 12 h light/dark cycle (light on at 8.00 p.m.) for 2 weeks before experimentation. Tap water and food pellets were available ad libitum.

Drugs: Iloperidone, paliperidone, loxapine, serotonin, adenosine triphosphate, noradrenaline, and potassium chloride were obtained from Sigma Chemicals (St Louis, Mo, USA). All drugs were dissolved in 0.9 % physiological saline. Saline was used as the vehicle controls. Loxapine, iloperidone, and paliperidone were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. Drugs were prepared freshly on the day of the experiment.

Experimental Design: The mice were randomly divided into experimental groups (n=7) as follows: saline; iloperidone 0.5 mg/kg; iloperidone 1 mg/kg; paliperidone 0.25 mg/kg; paliperidone 0.5 mg/kg, loxapine 2.5 mg/kg; loxapine 5 mg/kg. Chronic treatment was carried out by intraperitoneal drug injection (i.p.) for 21 days. The control group mice were received ip (0.9% saline) during the experiment.

Mice were sacrificed by decapitation after 21 days of treatment, followed by the removal of vas deferens from each side. Later, each vas deferens were separated into prostatic and epididymal portions of 1 –2 cm in length defined by Ventura (1998).

Epididymal and prostatic portions of vas deferens were surgically dissected free and soaked in 20 mL organ baths containing Krebs'solution with a composition (mM): 113 NaCl, 4.8 KCl, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgSO_4$, 25 $NaHCO_3$, 11.7 glucose equilibrated with 95%O_2 /5%CO_2 at 37°C during the

study. The upper end of the tissues was attached to an isometric force transducer (FDT 10 A Commat Iletisim, Ankara, Turkey) to measure the isometric force, and the lower end was fixed. Changes in isometric tension were 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) capable of analyzing data.

Equilibration was done that each strip was exposed with a basal tension of 1 g for 1 hour was done after the assembly. At the end of the equilibration, the strips were depolarized in Krebs solution with 80 mM KCl and left to equilibrate for 30 minutes. The Krebs Henseleit solution was replaced with a new solution every 15 minutes. After equilibration, the concentration–response curves to serotonin (10^8 to 10^4 M), NA (10^8 to 10^4 M) and ATP (10^8 to 10^4 M) were obtained cumulatively. Each response was expected to plateau, then the next drug bolus was added. After the concentration-response graphs of the drugs were completed, the tissues were washed for another 30 minutes.

Analysis of Data: Results are expressed as the mean±standard error mean (S.E.M.) of different experiments. Contractile responses to serotonin, ATP and noradrenaline were calculated as a percentage of the maximal contraction caused by KCl (80 mM). Statistical comparison between the groups was performed by GraphPad Prism 9 statistical program using ANOVA supported by Dunnett's post hoc test. Results were considered to be significantly different at a p-value of <0.05.

RESULTS

We showed that serotonin-induced contractions were significantly increased and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) groups compared with the control group, epididymal data are shown in figure ($p<0.05$; Figure 1). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from iloperidone treated groups than in the control group ($p<0.05$; Table 1). The Emax value for ATP was significantly lower in prostatic and epididymal portions of the mice vas deferens obtained from iloperidone treated groups than in the control group ($p< 0.05$; Table 1).

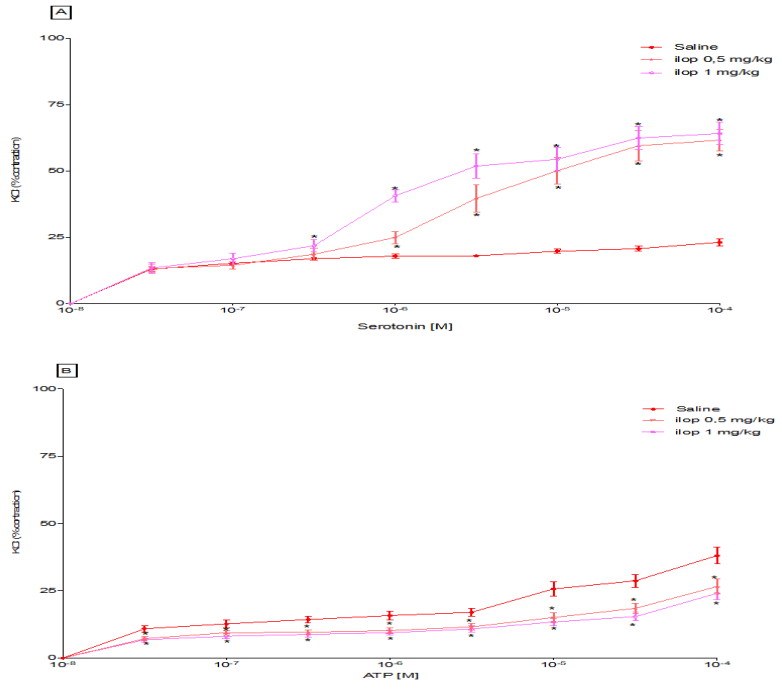

Figure 1. A: Serotonin concentration-responses curves of iloperidone in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of iloperidone in the isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). ilop: iloperidone; * $p< 0.05$.

Table 1. The Emax (% of 80 mM KCl) values for serotonin, noradrenaline, and ATP, and Emax value (mg) for 80 mM KCl in vas deferens obtained from iloperidone, paliperidone, and loxapine treatment and control mice

	Control	Ilop 0.5	Ilop 1	Pali 0.25	Pali 0.5	Lox 2.5	Lox 5
epididimal							
KCl	1534±184	1412±166	1394±212	1296±234	1498±241	1462±176	1386±198
serotonin	23±2	64±5*	66±6*	71±7*	74±7*	48±4*	53±5*
ATP	38±4	28±3*	24±3*	26±3*	21±2*	30±3*	28±3*
NA	42±4	41±4	40±4	40±4	39±4	44±4	42±4
prostatic							
KCl	2044±314	1984±216	1896±228	1998±224	2034±246	2156±292	2324±286
serotonin	16±2	36±4*	40±4*	32±3*	34±3*	27±3*	28±3*
ATP	28±3	22±2*	19±2*	15±2*	14±2*	18±2*	16±2*
NA	19±2	16±2	15±2	18±2	17±2	17±2	16±2

Data are the mean ± standard error of the mean (SEM). NA: noradrenaline; KCl: potassium chloride; ilop: iloperidone, pali: paliperidone, lox: loxapine; * p< 0.05.

Also, serotonin-induced contractions were significantly increased and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from paliperidone (0.25 and 0.5 mg/kg) groups compared with the control group, epididymal data are shown in figure (p<0.05; Figure 2). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from paliperidone treated groups than in the control group (p<0.05; Table 1). The Emax value for ATP was significantly lower in prostatic and epididymal portions of the mice vas deferens obtained from paliperidone treated groups than in the control group (p< 0.05; Table 1).

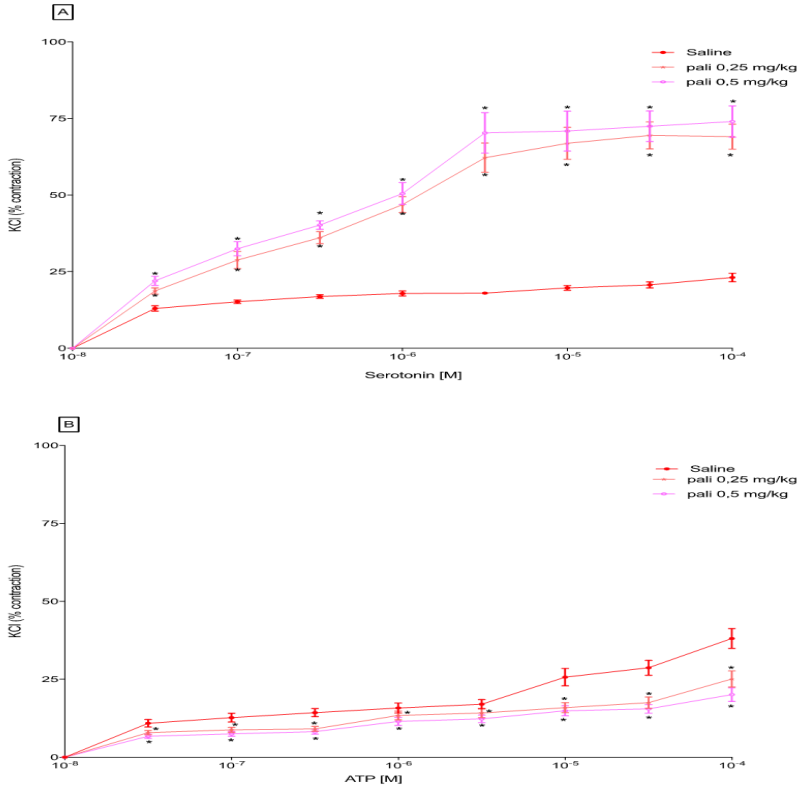

Figure 2. A: Serotonin concentration-responses curves of paliperidone in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of paliperidone in the isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). pali: paliperidone; * p< 0.05.

In addition, serotonin-induced contractions were significantly increased, and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from loxapine (2.5 and 5 mg/kg) groups compared with the control group, epididymal data are shown in figure ($p<0.05$; Figure 3). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from loxapine treated groups than in the control group ($p<0.05$; Table 1). The Emax value for ATP was significantly lower in prostatic and epididymal portions of the mice vas deferens obtained from loxapine treated groups than in the control group ($p<0.05$; Table 1).

The results of the study demonstrated that, iloperidone (0.5 and 1 mg/kg), paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) treatments had no effect on the noradrenaline-induced contractile responses in either portion of the vas deferens. The Emax value for noradrenaline had no effect in iloperidone, paliperidone and loxapine-treated groups than in the control group ($p>0.05$; Table 1).

There were no significant differences in KCl-

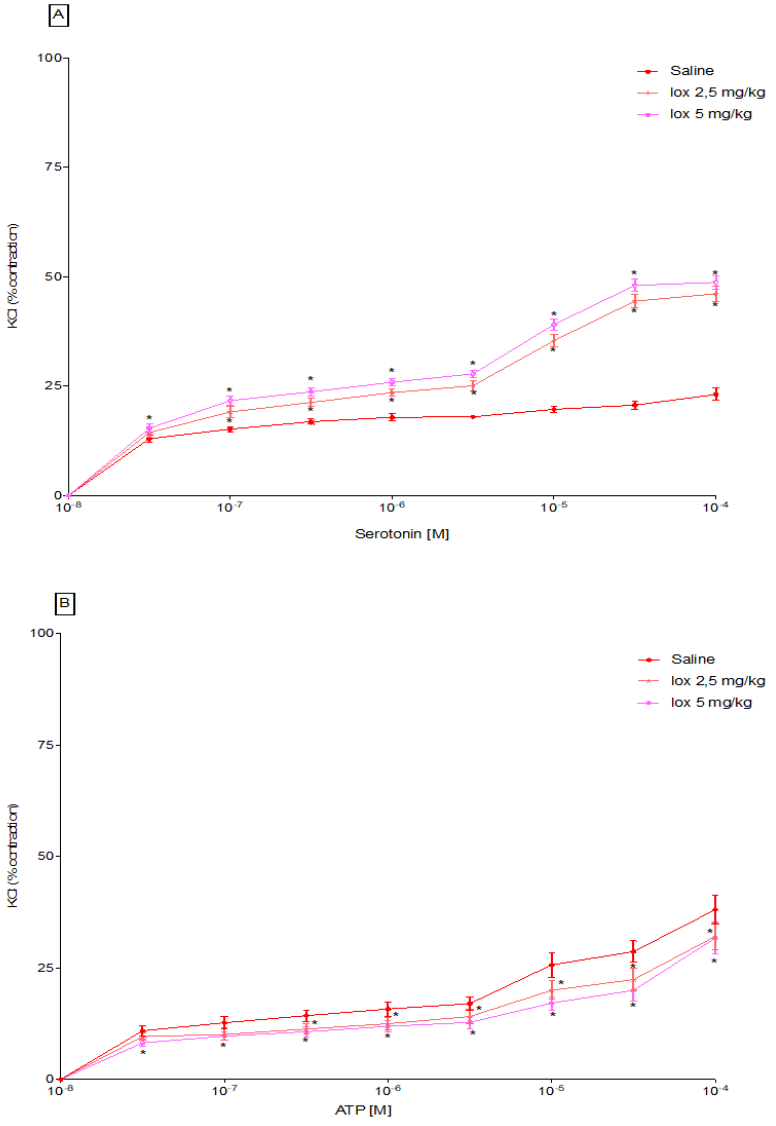

Figure 3. A: Serotonin concentration-responses curves of loxapine in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of loxapine in the isolated epididymal segment of mice vas deferens smooth muscle Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). lox: loxapine; * $p< 0.05$.

induced contractile responses among the groups.

DISCUSSION AND CONCLUSION

Psychological, pharmacological, traumatic, and hormonal factors are the cause of premature ejaculation. Erectile dysfunction is characterized by sexual reluctance, erectile dysfunction, orgasmic disorders, premature ejaculation, and/or painful ejaculation can be congenital or acquired, pervasive or situational, psychological, organic, or combined.[14] Neurological diseases such as autonomic neuropathy, Parkinson's disease, spinal cord trauma, usage of antihypertensive, antipsychotic, antidepressant, and alpha-blocker drugs, bladder, neck, and prostate diseases may cause sexual disorders. Premature ejaculation may be psychological or organic. For treatment of premature ejaculation, psychosexual and behavioural therapy, topical applications, antidepressants, alpha-blockers and/or sildenafil are used. Delayed ejaculation is usually psychological and may occur after SSRI usage, neuropathy, and spinal trauma.[15]

The importance of 5-HT pathways in the control of male sexual function has been demonstrated in previous publications. 5-HT is an inhibitory transmitter in the control of sex drive and high levels of 5-HT are associated with ejaculation inhibition. Therefore, SSRIs can be the therapy of choice for premature ejaculation because they can cause a slowing of ejaculation.[16]

In our study, we investigated the effects of iloperidone, paliperidone, and loxapine on vas deferens. Serotonin-induced contractions were significantly increased in both prostatic and epididymal portion of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) groups compared with the control group. SSRT inhibitors impair sexual function demonstrated in a previous study.[17] The reason for this deterioration is the disruption of the erectile pathways in the spinal cord with the increase of 5-HT receptors.[18]

ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) groups compared with the control group. On the other hand, iloperidone, paliperidone, and loxapine treatments had no significant effect on NA- and KCl-induced contractions of the prostatic and epididymal portions of the mice vas deferens. It is assumed that the contraction caused by potassium is 100% contraction, the contractions of vas deferens are evaluated according to this; these contractions are calculated as the percentage of potassium. We use potassium to test if there is a problem in the contractile mechanisms of the tissue. And also, the lack of effect of iloperidone, paliperidone or loxapine treatment on NA-induced contractions may be explained by serotonergic receptors or postreceptor mechanisms being more sensitive to these treatments than noradrenergic receptors or postreceptor mechanisms.

In summary, loxapine, iloperidone, and paliperidone increased serotonin response and decreased ATP response. These results may show the effect of these drugs on male reproductive function in patients using antipsychotic drugs. In addition, these drugs can be used in the treatment of delayed ejaculation, as they stimulate ejaculation by stimulating 5-HT neurons. Further studies can be done on this subject.

Ethics Committee Approval: Our study was approved by the Kocaeli University Local Ethics Committee for Animal Experiments (Date: 22.07.2014, decision no: KOÜ HADYEK 7/4-2014).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – MHT, MEB; Supervision – MHT, MEB, PT; Materials – MHT, MEB, PT; Data Collection and/or Processing – MHT, MEB, PT, RKK, ŞNBB; Analysis and/ or Interpretation – OM, FYA, BFE, GU; Writing – MHT, MEB, PT.

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