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Chronic Effects of Quetiapine, Paliperidone, Iloperidone and Loxapine on Mice Isolated Detrusor Smooth Muscle

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ABSTRACT

Objective: *Quetiapine, paliperidone, iloperidone, and loxapine are used for the treatment of patients with schizophrenia, the current study aimed to identify the effects of atypical antipsychotic drugs quetiapine, paliperidone, iloperidone, and loxapine in mice isolated bladder using the organ bath system.* ***Methods:*** *63 male inbred mice were used in this study. Mice were treated by i.p. injection of drugs for 21 days. Then, the effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-induced contractions in isolated detrusor strips. First, the detrusor strips were stimulated with KCl, and then tissues were washed for a further 30 min and pre-contracted with a submaximal concentration of carbachol. After the contraction reached the plateau, cumulative concentration-response curves to isoproterenol were obtained. The significance of differences was tested by one-way ANOVA with a Tukey post hoc test.* ***Results:*** *We showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from quetiapine, paliperidone, iloperidone, and loxapine treated group. However, none of the drug treatments showed an effect on the KCl responses of mice bladder.* ***Conclusion:*** *Quetiapine, paliperidone, iloperidone, and loxapine increased the isoproterenol-induced relaxations of the detrusor smooth muscle that increased the bladder capacity. We demonstrate that quetiapine, paliperidone, iloperidone, and loxapine may represent a potential drug for patients with overactive bladder. These drugs might be clinically useful for the treatment of overactive bladder in patients that should use antipsychotic drugs. These findings open a new approach to developing drugs for overactive bladder in the future.*

Keywords: Quetiapine, Paliperidone, Iloperidone, Loxapine, Overactive bladder, Mice

INTRODUCTION

Urination physiology is a complex event. Central micturation is controlled by the cerebral cortex, paraventricular nucleus, medial preoptic area, hypothalamus periaqueductal grey, and especially the pontine voiding center in the brain. Peripheral innervation; sympathetic nerves originate from T10-L2, parasympathetic nerves originate from S2-4 in the medulla spinalis. Somatic cholinergic motor nerves arise in S2-S4 motor neurons in Onuf's nucleus. All of these systems must work in full coordination [1,2].

When the bladder is empty, the bladder neck, urethra, and external urethral sphincter are contracted, while the detrusor is relaxed. When the bladder is full, stimuli start from the stretched urothelium *via.* thin myelinated A-delta fibers and ascend to the mesencephalic Periaqueductal Gray (PAG). Then the PAG sends excitatory input to Pontine Micturation Center (PMC). PMC sends stimuli *via.* descending fibers that inhibit the anufis nucleus [1,2].

Pathology in an overactive bladder is uncontrolled involuntary bladder contractions in the filling phase before the bladder is filled. Detrusor contractions occur with cholinergic M2 and M3 receptors, while relaxation occurs with

adrenergic β2 and β3 receptors. ATP and NO release in the urothelium trigger bladder contraction. Today, M2-3 effective anticholinergics and β3 agonist drugs are used in the treatment of overactive bladder [3].

The effects of potassium channels in detrusor on contraction and also the effects of the potassium channel subgroups like TREK-1 (KCNK2, K2P2.1), TREK-2 (KCNK2, K2P10.1), and TRAAK (KCNK4, K2P4.1) have been investigated. The effects of antipsychotics are especially through TREK-1 channels in the brain. It is known that TREK-1 is the cause of atypical discharges in epilepsy. It is known that TREK-1 is the main potassium channel in bladder smooth muscle. Detrusor over-activity associated with a decrease in functional TREK-1 channels has been demonstrated in an animal model with partial bladder outlet obstruction. Increased basal tone and increased spontaneous contractile activity in overactive detrusor specimens indicate that TREK-1 channels affect the bladder filling phase [4]. In our study, we used quetiapine, paliperidone, iloperidone, and loxapine that are used especially in the treatment of schizophrenia and we think these drugs may be altered urination functions.

Quetiapine, an atypical antipsychotic drug with dopamine D2 receptor and serotonin 5-HT2A receptor antagonizing activity used for various mental illnesses, such as schizophrenia and bipolar disorder [5,6]. The antidepressant activity of quetiapine may be mediated through noradrenaline transporter inhibition and partial 5-HT1A receptor agonism [7].

Paliperidone or 9-hydroxyrisperidone is the major active metabolite of risperidone. Its pharmacokinetics and mechanisms of action are thought to be similar to that of risperidone [8-10]. Paliperidone acts on dopamine D2 and serotonin 5HT2A receptors as an antagonist, exhibiting a high 5HT2A/D2 affinity ratio, like other atypical agents [11]. It also binds and antagonizes the α1- and α2-adrenergic receptors and H1-histaminergic receptors, but has almost no affinity for the cholinergic receptors [12,13].

Iloperidone is a second-generation ‘‘atypical’’ antipsychotic currently available as an oral formulation. Its primary mechanism of action is combined D2/5HT2A antagonism, with greater affinity for the 5HT2A receptor than for the D2 receptor [14]. Whereas iloperidone shares a high affinity for both D2 and 5HT2A receptors, it has a unique receptor-binding profile that includes a very strong affinity for the adrenergic α1-receptor [15].

Loxapine is a post-synaptic antagonist at the D2 receptor, dissociating at an intermediate rate, as well as an antagonist at the serotonin 5-HT2A receptor [16,17]. Based on human and animal studies, loxapine has a negligible affinity to glutamate N-Methyl-D-Aspartate (NMDA) receptors [18]. Other pharmacologic effects include antagonism at histaminergic H1, cholinergic M1, and adrenergic α1 receptors, which may be responsible for side effects including somnolence, anticholinergic effects, and orthostatic hypotension [19].

Loxapine binds to the D4 receptor with higher affinity than to other dopaminergic receptors in human and animal models [20]. Also, loxapine has effects on Na-K and K-ATP channels, inhibits TREK1 and TREK2 of K channels [21].

With this background; the current study aimed to investigate the effects of atypical antipsychotic drugs quetiapine, paliperidone, iloperidone, and loxapine on urinary bladder contractions after chronic drug use *in vitro*.

MATERIALS AND METHODS

Animals

Sixty-three 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. All procedures involving animals complied 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 and Therapeutic Agents

Quetiapine, paliperidone, iloperidone and loxapine, carbachol, isoproterenol, papaverine, 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 control. Quetiapine, paliperidone, iloperidone, and loxapine 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

Sixty-three male inbred BALB/c ByJ mice randomly divided into nine experimental groups (n=7) as follows: saline, quetiapine 5 mg/kg, quetiapine 10 mg/kg, paliperidone 0.25 mg/kg, paliperidone 0.50 mg/kg, iloperidone 0.5 mg/kg, iloperidone 1 mg/kg, loxapine 2.5 mg/kg, loxapine 5 mg/kg, Mice were treated by IP injection of drugs during 21 days. Mice receiving only the vehicle (0.9% saline, i.p.) during 21 days served as a control group. After removing adhering fat and connective tissue, the bladder was opened and divided into longitudinal strips, weighed, and placed in physiological saline solution of the following composition (mmol/l): NaCl 118; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ 1.2; KH_2PO_4 1.18; $NaHCO_3$24.88; glucose 5.55. The DSM strips were suspended in a 10 ml water-jacketed (37°C) tissue bath, containing physiological saline solution continuously gassed with 95% O_2 and 5% CO_2, resulting in a pH of 7.4. The resting tension on the tissues was maintained at 1 g during which the solution was replaced for 15 min intervals before adding drugs. 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 (ACQ 4.0 Biopac Systems Inc. Goleta) that also could 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 h, with the Krebs Henseleit solution replaced every 15 min with fresh solution. At the end of the equilibration, strips were depolarized with 80 mM KCl in Krebs solution and allowed to equilibrate for 30 min. Then, the effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-induced contractions in isolated detrusor strips. First, the detrusor strips were stimulated with 80 mM KCl, and then tissues were washed for a further 30 min and pre-contracted with a submaximal concentration of carbachol (3×10^6 M). After the contraction reached a plateau, cumulative concentration-response curves to isoproterenol (10^8 to 10^4 M) then papaverine (10^4 M) were obtained.

Analysis of Data

Results are expressed as the mean ± S.E.M. of different experiments. Relaxation responses to isoproterenol are calculated as a percentage of the maximal relaxation caused by papaverine (10^4 M). The significance of differences was tested by one-way ANOVA with a post-hoc Tukey's-Kramer test. Results were considered to be significantly different at a p-value of <0.05.

RESULTS

We showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from the atypical antipsychotic drug quetiapine treated group shown in Figure 1. However, quetiapine treatment did not affect the KCl responses of mice bladder.

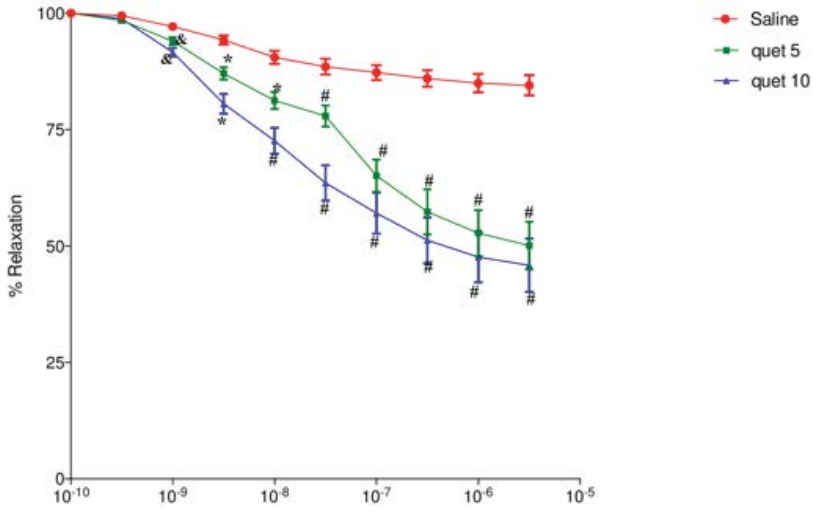

Figure 1 Isoproterenole concentration-responses curves in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation induced by papaverine (10^4 M) is given as the mean ± standard error of the mean (SEM)

Then we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from atypical antipsychotic drug paliperidone treated group shown in Figure 2. However, paliperidone treatment did not affect KCl responses of mice bladder.

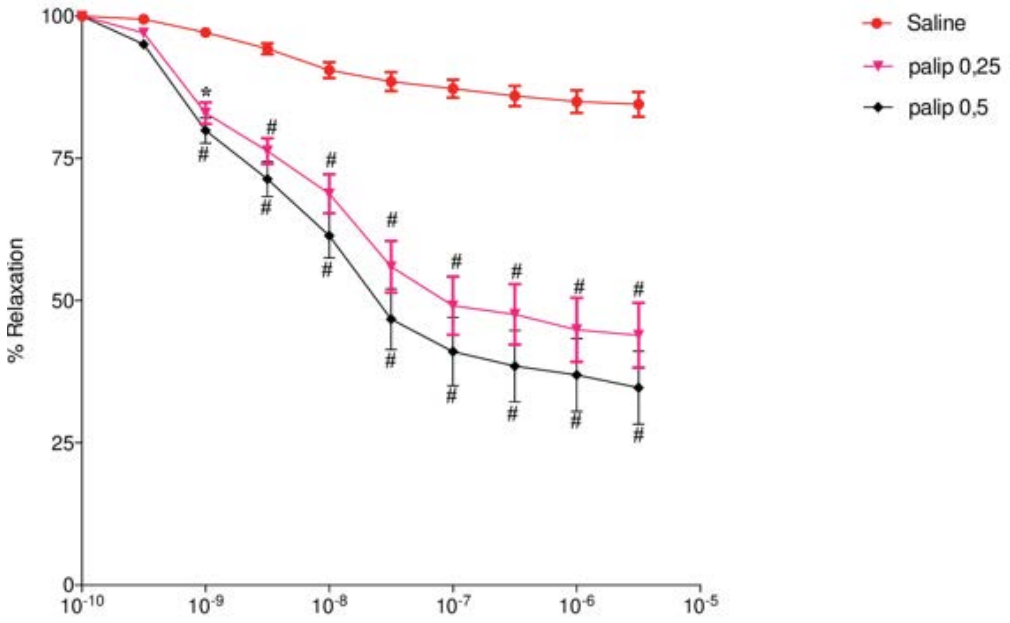

Figure 2 Isoproterenole concentration-responses curves in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation induced by papaverine (10^4 M) is given as the mean ± standard error of the mean (SEM)

Also, we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from the atypical antipsychotic drug iloperidone treated group shown in Figure 3. However, iloperidone treatment did not affect KCl responses of mice bladder.

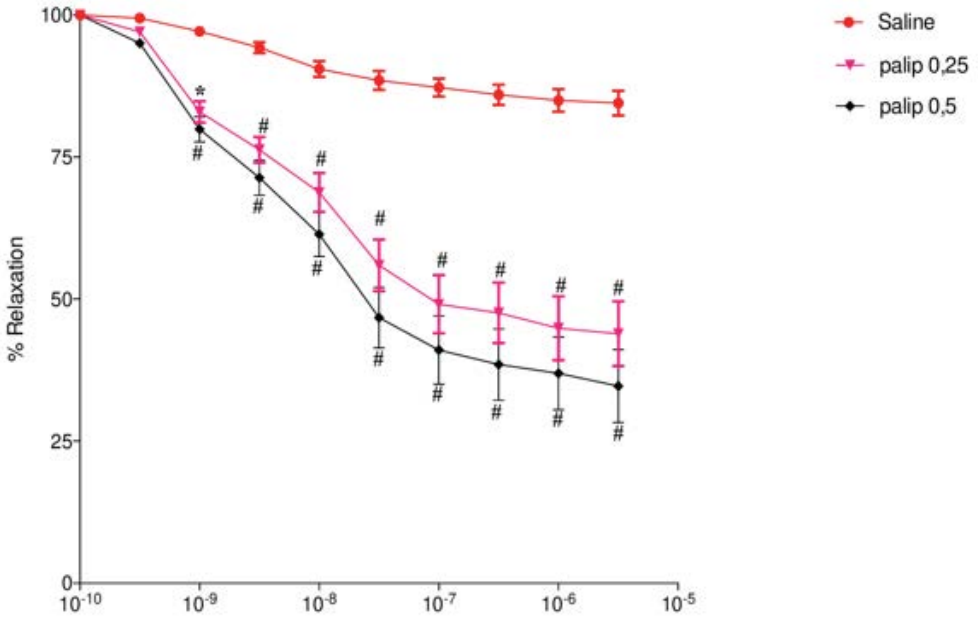

Figure 3 Isoproterenole concentration-responses curves in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation induced by papaverine (10^4 M) is given as the mean ± standard error of the mean (SEM)

Then we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from atypical antipsychotic drug loxapine treated group shown in Figure 4. However, loxapine treatment did not affect KCl responses of mice bladder.

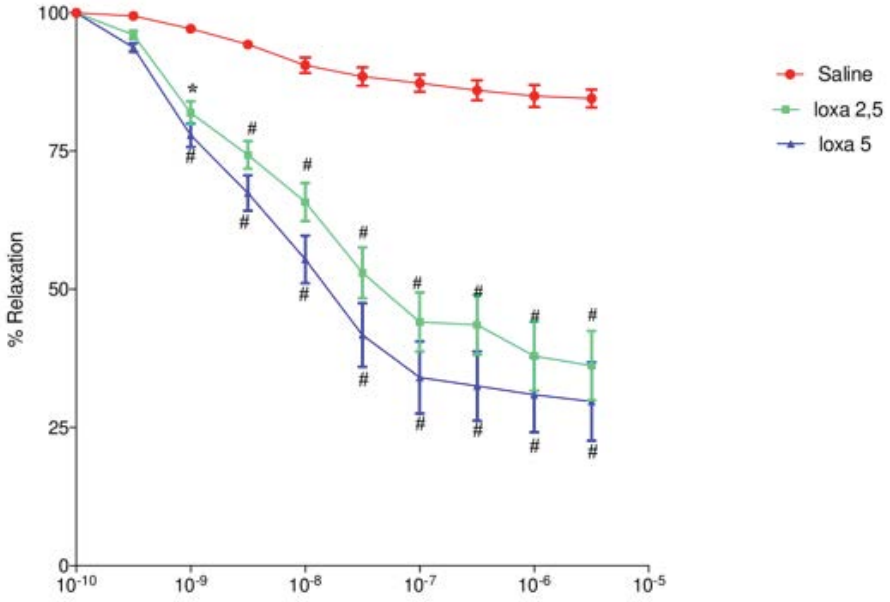

Figure 4 Isoproterenole concentration-responses curves in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation induced by papaverine (10^4 M) is given as the mean ± standard error of the mean (SEM)

There were no significant differences in KCl-induced contractile responses among the groups.

DISCUSSION

Several physiopathologic conditions lead to the manifestation of the Overactive Bladder (OAB). These conditions include aging, diabetes mellitus, bladder outlet obstruction, spinal cord injury, stroke and brain injury, Parkinson's disease, multiple sclerosis, interstitial cystitis, stress, and depression [22].

The antipsychotic drugs have complex receptors affinity; they include dopamine, serotonin, histamine, glutamate. Quetiapine, dopamine D2 receptor, and serotonin 5-HT2A receptor antagonizing activity [5,6]. The antidepressant activity of quetiapine may be mediated through noradrenaline transporter inhibition and partial 5-HT1A receptor agonism [7]. Paliperidone is a dopamine D2 and serotonin 5HT2A receptors antagonist, like other atypical agents [11]. It also binds and antagonizes the α1- and α2-adrenergic receptors and H1-histaminergic receptors. Iloperidone is a D2 and 5HT2A receptors antagonist; it has a unique receptor-binding profile that includes a very strong affinity for the adrenergic α1-receptor [15].

Loxapine is an antagonist at the D2 receptor and 5-HT2A receptor [16,17]. Based on human and animal studies, loxapine has a negligible affinity to glutamate N-Methyl-D-aspartate (NMDA) receptor [18]. Other pharmacologic effects include antagonism at histaminergic H1, cholinergic M1, and adrenergic α1 receptors.

The effects of potassium channels and potassium channel subgroups like TREK-1, TREK-2, and TRAAK have been investigated in detrusor on contraction. It is known that TREK-1 is the main potassium channel in bladder smooth muscle. Detrusor overactivity associated with a decrease in functional TREK-1 channels has been demonstrated in an animal model with partial bladder outlet obstruction. Increased basal tone and increased spontaneous contractile activity in overactive detrusor specimens indicate that TREK-1 channels affect the bladder filling phase [23].

Antipsychotics act through receptors such as D1, D3, and H1, especially D2 and 5-HT2. In the last decade, there are

studies on its effect, especially on potassium channels. And also, the effects of antipsychotics are especially through TREK-1 channels in the brain. Diseases such as schizophrenia, epilepsy, agitation, bipolar disorder are treated with TREK-1 effective drugs, especially a type of potassium channel. In recent studies, it has been shown that the most common potassium channel in detrusor is TREK-1 [24].

TREK-1 and TREK-2 belong to the two-pore domain K^+ (K2P) family. These channels, which are usually independent of voltage or weakly voltage-dependent, contribute to the resting membrane potential as a leak-type K^+ conductance. Membrane stress, pH, temperature, some neurotransmitters, and unsaturated fatty acids show marked activation in response to various physicochemical stimuli. Antipsychotics specifically inhibit TREK-1. They probably cause relaxing in the detrusor due to this inhibition [25]. Although it is known that the antipsychotic drugs that we used cause urinary retention, they weren't investigated on bladder smooth muscle contractions.

Antipsychotics specifically inhibit TREK-1 in a dose-dependent and reversible manner. TREK-1 channels were thought to be effective in the bladder filling phase due to increased basal tone and spontaneous contractile activity with overactive detrusor specimens. Gene and protein analysis of the K2P channels TREK-1, TREK-2, and TRAAK in the human bladder revealed that TREK-1 is the predominantly expressed member of the mechano-gated subfamily of K2P channels [24].

In a recent study, in rats with partial bladder outlet obstruction and secondary overactive detrusor, TREK-1 receptor upregulation was detected in the dorsal root ganglia which reduce the overactive detrusor [25].

CONCLUSION

In conclusion; in our study, we used antipsychotic drugs such as quetiapine, paliperidone, iloperidone, and loxapine. These antipsychotic drugs increased the isoproterenol-induced relaxations of the detrusor smooth muscle that increased the bladder capacity. We found that these drugs cause relaxation in the bladder muscle. We think that these effects of drugs may be mainly acting through both dopamine and serotonin receptors antagonist and TREK-1 channels. We demonstrate that these antipsychotics may represent a potential drug for patients with overactive bladder. These drugs might be clinically useful for the treatment of overactive bladder in patients that should use antipsychotic drugs. These findings open a new approach to developing drugs for overactive bladder in the future.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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