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Haloperidol, Olanzapin, Risperidon ve Klozapinin Organ Banyosu Sistemi Kullanılarak Fare Detrusor Kası Üzerine Etkileri

Effects of Haloperidol, Olanzapine, Risperidone And Clozapine on Mice Detrusor Muscle Using Organ Bath System

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ÖZ

Amaç: Mesane normalde dolum fazı sırasında herhangi bir kasılma veya aktivite göstermez. Aşırı aktif mesanede, dolum aşamasında spontan kasılmalar ve detrüsör instabilitesi görülür ve idrar kaçırma meydana gelir. Bu çalışma, birinci kuşak antipsikotik olan haloperidol ve ikinci kuşak antipsikotikler olan olanzapin, risperidon ve klozapinin, organ banyosu sistemi kullanılarak izole edilmiş fare mesanesi üzerindeki etkilerini göstermeyi amaçlamaktadır.

Materyal ve Metot: 63 tane kendi içinde yetiştirilmiş erkek fareye salin, haloperidol 0,125 mg/kg, haloperidol 0,25 mg/kg, olanzapin 1 mg/kg, olanzapin 2 mg/kg, risperidon 0,25 mg/kg, risperidon 0,5 mg/kg, klozapin 1,25 mg/kg ve klozapin 2,5 mg/kg uygulandı ve gruplara ayrıldı. Fareler 21 gün boyunca ilaçlarla tedavi edildi. Daha sonra, izole edilmiş fare detrüsör şeritlerinde karbakol ile indüklenen kasılmaların, izoproterenol ile indüklenen gevşeme tepkileri üzerinde ilaçların etkileri araştırıldı.

Bulgular: Olanzapin, risperidon ve klozapin ile tedavi edilen gruplardan elde edilen fare detrüsör şeritlerinde karbakol kaynaklı kasılmaların, izoproterenol ve papaverin tarafından gevşediğini gösterdik. Gruplar arasında KCl'nin neden olduğu kasılma tepkilerinde önemli bir fark yoktu.

Sonuç: Olanzapin, risperidon ve klozapin, mesane kapasitesini artıran detrusor kasının izoproterenol kaynaklı gevşemelerini arttırdı. Bu ilaçlar, antipsikotik ilaç kullanması gereken hastalarda aşırı aktif mesane tedavisinde klinik olarak faydalı olabilir.

Anahtar Kelimeler: Aşırı aktif mesane, haloperidol, klozapin, olanzapin, risperidon

ABSTRACT

Objective: The bladder normally shows no contractility or activity during the filling phase. In the overactive urinary bladder, spontaneous contractions and detrusor instability are seen in the filling phase and urinary incontinence occurs. This study aims to demonstrate the effects of first-generation antipsychotic haloperidol and second-generation antipsychotics olanzapine, risperidone, and clozapine on mice isolated bladder using the organ bath system.

Materials and Methods: 63 male inbred mice were divided as saline, haloperidol 0.125 mg/kg, haloperidol 0.25 mg/kg, olanzapine 1 mg/kg, olanzapine 2 mg/kg, risperidone 0.25 mg/kg, risperidone 0.5 mg/kg, clozapine 1.25 mg/kg and clozapine 2.5 mg/kg groups. Mice were treated with drugs for 21 days. Then, the effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-induced contractions in isolated detrusor strips.

Results: We showed that carbachol-induced contractions relaxed by isoproterenol and papaverine in mice detrusor strips obtained from olanzapine, risperidone, and clozapine treated groups. There were no significant differences in KCl-induced contractile responses among the groups.

Conclusion: Olanzapine, risperidone, and clozapine increased the isoproterenol-induced relaxations of the detrusor muscle that increased the bladder capacity. These drugs might be clinically useful for the treatment of overactive urinary bladder in patients that should use antipsychotic drugs.

Keywords: Clozapine, haloperidol, olanzapine, overactive urinary bladder, risperidone

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INTRODUCTION

Overactive urinary bladder has a high prevalence. Although it can be seen in all age groups and in both sexes, symptoms generally increase with age. The most prominent symptom of overactive urinary bladder is urgency.[1]

The normal function of the urinary bladder is controlled by the central and peripheral nervous systems. These two systems must work in harmony for the bladder to function properly. Unfortunately, some problems such as emotional distress, anxiety, depression, sleep disturbances and issues with sexuality, and avoiding social relationships may occur in patients. In addition, it has been suggested that there is a relationship between depression and anxiety associated with overactive urinary bladder and urgency incontinence and nocturia.[2]

Haloperidol exerts its effects through dopamine D2 receptors which are targets for antipsychotic drugs.[3] It is shown that olanzapine has high affinity for 5-HT2A/2C, dopamine receptors D1–4, M1–5 muscarinic receptors, H1 histaminergic receptors and α-1 receptors.[4] Other atypical antipsychotic clozapine also affects some receptors, including dopamine D4, serotonin 5-HT2A, and 5-HT2C, α1- and α2-adrenergic, cholinergic, and histamine H1, similar to olanzapine.[5] Risperidone is also currently used in the treatment of psychiatric diseases. The main pharmacological activities of risperidone are shown its effects mediated by antagonism of serotonergic 5-HT2A and dopaminergic D2 receptors.[6]

The atypical antipsychotics such as olanzapine, risperidone and clozapine that we used in this study; the incidence of extrapyramidal side effects is lower than classical antipsychotics such as haloperidole. It is more effective in curing the negative symptoms of schizophrenia and is used in the treatment of schizophrenia unresponsive to classical neuroleptics. Therefore, we aimed to demonstrate whether the long-term use of first-generation antipsychotic haloperidol and second-generation antipsychotic risperidone, olanzapine and clozapine may affect the contraction-relaxation responses on the detrusor muscle, in vitro in mice.

MATERIALS AND METHODS

Ethical Status: All procedures ũnvolvũng anũmals complied 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 Kocaeli, Turkey). All authors comply with NIH guidelines for use of laboratory animals.

Animals: Male ũnbred BALB/c ByJ mũce (Anũmal 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: Haloperũdol, olanzapũne, rũsperũdone, clozapine, 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. Haloperidol, olanzapine, risperidone and clozapine 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: They randomly divided into five experimental groups (n=7) as follows: saline; haloperidol 0.125 mg/kg, haloperidol 0.25 mg/kg, olanzapine 1 mg/kg, olanzapine 2 mg/kg, risperidone 0.25 mg/kg, risperidone 0.5 mg/kg, clozapine 1.25 mg/kg and clozapine 2.5 mg/kg.We determined the doses of drugs from the previous studies.[7,8] Mice were treated by i.p. injection of haloperidol, olanzapine, risperidone or clozapine for 21 days.[8] Mice receiving only the vehicle (0.9% saline, i.p.) during 21 days served as the 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; CaCl2 2.5; MgSO4 1.2; KH2PO4 1.18; NaHCO324.88; glucose 5.55. The detrusor smooth muscle strips were suspended in a 10-ml water-jacketed (37 ◦C) tissue bath, containing physiological saline solution continuously gassed with 95% O2and 5% CO2, 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 (ACQ4.0 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 80mM KCl, then tissues were washed for a further 30 min and precontracted 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 3.10^{-4} M) then papaverine (10^{-4} M) were obtained.

Analysis of Data: Statistical analysis of the data procured from the tests was made by Graphpad Prism 9 statistical program. Results are expressed as the mean ± S.E.M. of different experiments. Relaxation responses to isoproterenol calculated as 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

The findings of the study clearly showed that carbachol-induced contractions significantly don't relaxed by isoproterenol (10−8 to 3.10−4 M) then papaverine in mice detrusor strips obtained from haloperidole treated group in Figure 1. However haloperidole treatment had no effect on KCl responses of mice bladder.

Results of isolated organ bath experiments demonstrated that carbachol-induced contractions relaxed by isoproterenol (10^{-8} to 3.10^{-4} M) then papaverine in mice detrusor strips obtained from atypical neuroleptic drug olanzapine treated group shown in Figure 2. However, olanzapine treatment had no effect on KCl responses of mice bladder.

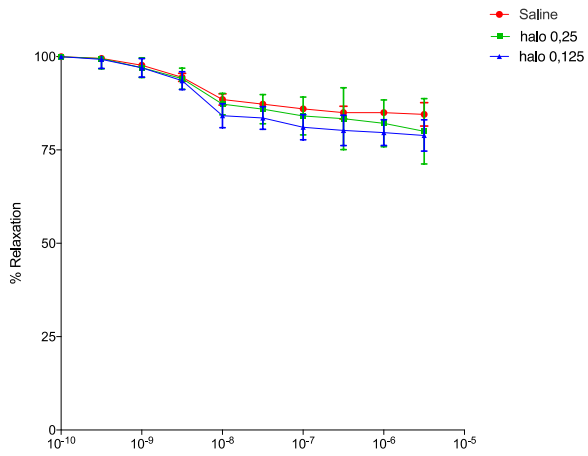

Figure 1. Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine (10^{-4} M) is given as the mean ± standart error of the mean (SEM). Number of mice in each group is 7.

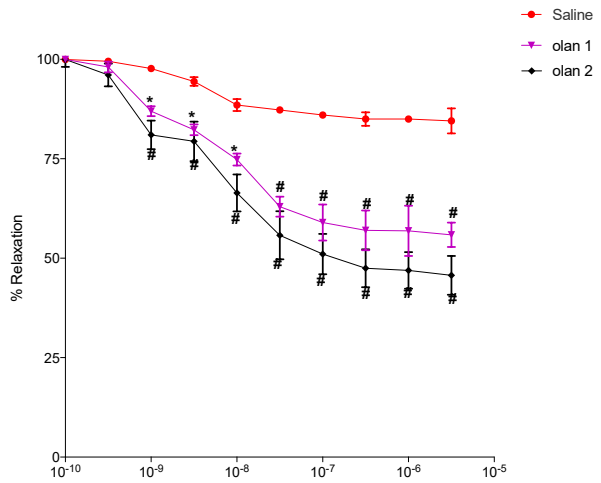

Figure 2. Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation(shown in y-axis) induced by papaverine (10^{-4} M) is given as the mean ± standart error of the mean (SEM). Number of mice in each group is 7. (* = p<0,05), (# = p<0,001)

In addition we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol (10^{-8} to 3.10^{-4} M) in mice detrusor strips obtained from atypical neuroleptic drugs risperidone and clozapine treated group shown in Figure 3 and Figure 4, respectively. However, neither risperidone nor clozapine treatment had no effect on KCl responses of mice bladder. In this research, the ranking of their relaxing potencies of the mice detrusor strips was clozapine > olanzapine > risperidone. Also, there were no significant differences in KCl-induced contractile responses among the groups.

DISCUSSION AND CONCLUSION

Normally, there is no activity in the bladder during the filling phase, but strong contractions of the bladder are seen when starting to urinate. These contractions continue until the bladder is completely empty. In an overactive bladder, spontaneous contractions and detrusor hyperreflexia occur during the filling phase. Incontinence can occur when these contractions are severe and cannot be prevented.[9,10]

In overactive urinary bladder syndrome, detrusor contractions begin before the bladder is filled. This situation causes the bladder to be emptied before it is filled and frequent urination.[11] The overactive

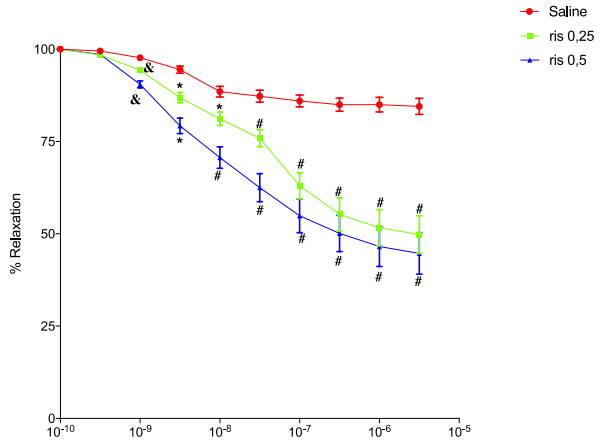

Figure 3. Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine (10^{-4} M) is given as the mean ± standart error of the mean (SEM). Number of mice in each group is 7. (& = p<0,05), (* = p<0,01), (# = p<0,001)

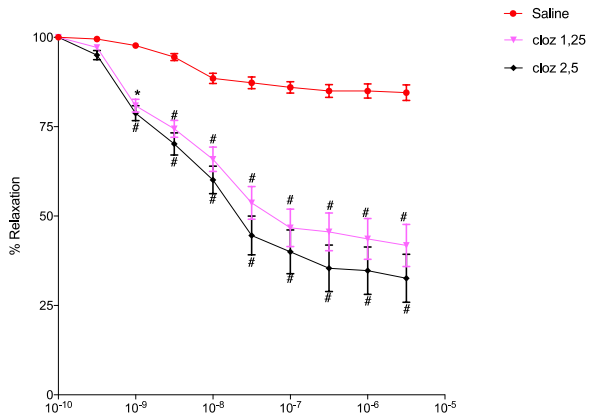

Figure 4. Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation(shown in y-axis) induced by papaverine (10^{-4} M) is given as the mean ± standart error of the mean (SEM). Number of mice in each group is 7. (* = p<0,05), (# = p<0,001)

urinary bladder is a complex illness. It involves both peripheral and central nervous system factors.[12,13] All the drugs we use in practice today are peripheral acting agents. And there is not enough data and studies on central-acting drugs.

Antimuscarinic and beta 3 mimetic agents are used in first-line pharmacotherapy to prevent contractions and detrusor hyperreflexia in the filling phase.[14] In the use of antimuscarinic, side effects such as dry mouth, constipation and blurred vision can be seen in a dose-dependent manner.

Voiding control is done by the pontine urination center. In the overactive urinary bladder, contractions also occur beyond the control of this center.[15]

This study clearly showed that carbachol-induced contractions significantly don't relaxed by isoproterenol (10−8 to 3.10−4 M) then papaverine in mice detrusor strips obtained from haloperidole treated group; on the other hand we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol (10−8 to 3.10−4 M) in mice detrusor strips obtained from atypical neuroleptic drugs olanzapine, risperidone and clozapine treated group. Atypical antipsychotic drugs olanzapine, risperidone, and clozapine were found to relax by directly affecting the bladder muscle outside the central system in our study. Its use as the first choice, especially in patients who need to use antipsychotics and have overactive urinary bladder, makes it possible to treat two diseases with a single drug. These findings may open a new perspective to develop drugs in the treatment of overactive urinary bladder in the future.

In conclusion; we showed that carbachol-induced contractions relaxed by isoproterenol then papaverine in mice detrusor strips obtained from atypical neuroleptic drug olanzapine, clozapine, risperidone treated group but not typical neuroleptic haloperidol. The findings of our study demostrated that olanzapine, risperidone and clozapine increased the isoproterenol-induced relaxations of the detrusor smooth muscle that increased the bladder capacity. We showed that olanzapine, risperidone, and clozapine may offer a potential drug for patients with overactive urinary bladder. Olanzapine, risperidone, and clozapine can be used alone or in combination with anticholinergic and beta 3 receptor agonists for the treatment of overactive urinary bladder to minimize side effects. These three drugs might be clinically useful for the treatment of overactive urinary bladder in patients that should use antipsychotic drugs.

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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