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Ziprasidon, Aripiprazol, Blonanserin, Siyamemazin ve Nemonaprid'in Farelerde İzole Detrusor Düz Kasına Kronik Etkileri

Chronic Effects of Ziprasidone, Aripiprazole, Blonanserin, Cyamemazine, and Nemonapride on Mice Isolated Detrusor Smooth Muscle

[1]Mehmet Hanifi TANYERI, [2]Mehmet Emin BUYUKOKUROGLU, [2]Pelin TANYERI, [2]Rumeysa KELES KAYA, [2]Şeyma Nur BASARIR BOZKURT, [3]Oğuz MUTLU, [3]Füruzan YILDIZ AKAR, [3]Bekir Faruk ERDEN, [3]Güner ULAK

[1]Yenikent Government Hospital, Department of Urology, 54100 Sakarya/Turkey
[2]Sakarya University, Faculty of Medicine, Department of Pharmacology, 54100-Sakarya/Turkey
[3]Kocaeli University, Faculty of Medicine, Department of Pharmacology, 41380-Kocaeli/Turkey

Mehmet Hanifi Tanyeri: https://orcid.org/0000-0003-2654-2724
Mehmet Emin Büyükokuroğlu: https://orcid.org/0000-0002-1452-3879
Pelin Tanyeri: https://orcid.org/0000-0002-2987-5834
Rümeysa Keleş Kaya: https://orcid.org/0000-0002-5554-1918
Şeyma Nur Başarir Bozkurt: https://orcid.org/0000-0002-2986-5089
Oğuz Mutlu: https://orcid.org/0000-0003-0952-0742
Füruzan Akar: https://orcid.org/0000-0003-0948-3857
Faruk Erden: https://orcid.org/0000-0002-2542-5158
Güner Ulak: https://orcid.org/0000-0002-6132-6712

ÖZ

Amaç: Ziprasidon, aripiprazol, blonanserin, siyamemazin ve nemonaprid şizofreni tedavisinde kullanılan atipik antipsikotik ilaçlardır. Bu çalışmada bu atipik antipsikotik ilaçların organ banyosu kullanılarak farelerde izole edilmiş mesane üzerine etkilerinin belirlenmesi amaçlanmıştır.

Materyal ve Metot: Fareler 21 gün boyunca intraperitoneal ilaç enjeksiyonu uygulandı. İlaçların izole detrusor şeritlerinde karbakolden kaynaklanan kasılmaların izoproterenol kaynaklı gevşeme tepkileri üzerindeki etkileri araştırıldı. Detrüsör şeritleri KCl ile uyarıldı, daha sonra dokular 30 dakika yıkandı ve submaksimal bir karbakol konsantrasyonu ile önceden kastırıldı. Kasılma belli bir platoya ulaştıktan sonra, izoproterenole kümülatif konsantrasyon-yanıt eğrileri elde edildi.

Bulgular: Karbakol kaynaklı kasılmaların ziprasidon, aripiprazol, blonanserin ve siyamemazin ile muamele edilen gruptan elde edilen fare detrusor şeritlerinde izoproterenol ile doza bağlı olarak gevşediğini gösterdik. Bununla birlikte, ilaç tedavilerinin hiçbiri, fare mesanelerinin KCl yanıtlarını etkilememiştir.

Sonuç: Nemonaprid dışında ziprasidon, aripiprazol, blonanserin ve siyamemazin, izoproterenol ile indüklenen detrüsör düz kas gevşemesi görülmesi mesane kapasitesini arttırabileceğini göstermektedir. Dört ilacın aşırı aktif mesane için potansiyel bir tedavi olabileceğini ön görmekteyiz. Bu ilaçlar, antipsikotikleri kullanması gereken hastalarda aşırı aktif mesane tedavisinde klinik olarak yararlı olabilir.

Anahtar Kelimeler: Aripiprazol, blonanserin, nemonaprid, siyamemazin, ziprasidon

ABSTRACT

Objective: Ziprasidone, aripiprazole, blonanserin, cyamemazine, and nemonapride are atypical antipsychotic drugs used for the treatment of schizophrenia. This study aimed to identify the effects of these atypical antipsychotic drugs in mice isolated bladder using the organ bath system

Materials and Methods: The mice were injected intraperitoneally with drugs for 21 days. The effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-induced contractions in isolated detrusor strips. The detrusor strips were stimulated with KCl, then tissues were washed for a further 30 min and precontracted with a submaximal concentration of carbachol. After the contraction reached a plateau, cumulative concentration-response curves to isoproterenol were obtained.

Results: We showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from ziprasidone, aripiprazole, blonanserin, and cyamemazine but not nemonapride treated group. However, none of the drug treatments had any effect KCl responses of mice's bladder.

Conclusion: Ziprasidone, aripiprazole, blonanserin, and cyamemazine but not nemonapride increased the isoproterenol-induced relaxations of the detrusor smooth muscle indicates that it can increase the bladder capacity. We demonstrate that four drugs may represent a potential treatment for overactive bladder. They might be clinically useful for the treatment of overactive bladder in patients that should use antipsychotics.

Keywords: Aripiprazole, blonanserin, cyamemazine, nemonapride, ziprasidone

Sorumlu Yazar / Corresponding Author:
Pelin Tanyeri
Sakarya University, Faculty of Medicine, Department of Pharmacology, 54100-Sakarya/Turkey
Tel: +(90) 530 512 55 90
E-mail: pelintanyeri@yahoo.com

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INTRODUCTION

The International Continence Society, with slight modification by the International Consultation on Incontinence Research Society, states that overactive bladder (OAB) syndrome is urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or obvious pathology.[1,2] Previous studies conducted in different countries have shown that the prevalence rate of OAB to be among 6%-%20,1 in both gender.[3]

Reflexes of the lower urinary tract, since bladder urine storage, require inhibition of the muscle such that disinhibition of bladder motility or voiding can be presumed to cause detrusor overactivity or urgency urinary incontinence.[4] OAB syndrome can often be described by patients also reporting functional problems, including altered bowel function.[5]

Pathology in OAB 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. Currently, M2-3 effective anticholinergics (oxybutynin, tolterodine, solifenacin, trospium chloride, propiverine.) and β3 agonist drugs are used in the treatment of OAB.[6]

Ziprasidone is indicated for the treatment of schizophrenia, bipolar disorder, and acute mania. Its affinities to serotonin 2A (5-HT2A), dopamine-2 (D2), 5-HT1A, 5-HT1D, and 5-HT2C receptors have been known.[7] Aripiprazole is a unique antipsychotic drug with a pharmacological profile different from other available antipsychotics that is considered to be a partial agonist at 5- HT1A and dopamine D2 receptors, and an antagonist at the 5- HT2A.[8] While it is possible to prevent an overactive bladder with the use of this active substance, there is also the possibility of causing enuresis.[9] The other antipsychotic agent Blonanserin has a high affinity for receptors D2 and 5-HT2A. It has also a low affinity for receptors of adrenergic α1, histaminergic H1, muscarinic M1, serotonergic 5-HT2C, 5-HT2A, and partial agonistic activity for 5-HT1A.[10,11] Among the known side effects of Blonanserin, there is already urinary retention. Naturally, people with an OAB will benefit from this side effect.[12] On the other hand, cyamemazine exerts antagonist activity for D2, 5-HT2A, 5-HT2C, and 5-HT3 receptors.[13] Nemonapride has highly selective dopamine D2, D3, and D4 receptors antagonist.[14]

We aimed to demonstrate that whether these antipsychotics may represent a potential drug for patients with OAB. With this background, the current study aimed to investigate the effects of atypical antipsychotic drugs ziprasidone, aripiprazole, blonanserin, cyamemazine, and nemonapride on urinary bladder contractions after chronic drug use in vitro.

MATERIALS AND METHODS

Animals and Ethical Status: Seventy-seven 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 (Date:22.07.2014, decision no: KOÜ HADYEK 7/4-2014).

Drugs: Ziprasidone, aripiprazole, blonanserin, cyamemazine, nemonapride, 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. Ziprasidone, aripiprazole, blonanserin, cyamemazine, and nemonapride 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. The drug doses were decided based on previous studies.[15-18]

Experimental Design: Seventy-seven male inbred BALB/c ByJ mice randomly divided into eleven experimental groups (n=7) as follows: saline, ziprasidone 0,5 mg/kg, ziprasidone 1 mg/kg, aripiprazole 3 mg/kg, aripiprazole 6 mg/kg, blonanserin 0,5 mg/kg, blonanserin 1 mg/kg, cyamemazine 0,25 mg/kg, cyamemazine 0,50 mg/kg, nemonapride 0,5

mg/kg, nemonapride 1 mg/kg. Mice were treated by i.p. injection of drugs for 21 days. Mice receiving only the vehicle (0.9% saline, i.p.) for 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 DSM strips were suspended in a 10 ml water-jacketed (37 ˚C) tissue bath, containing physiological saline solution continuously gassed with 95% O2 and 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 the 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 were given as mean ± SEM. Relaxation responses to isoproterenol are calculated as a percentage of the maximal relaxation caused by papaverine (10^{-4} M). Results were considered to be significantly different at a p-value of <0.05. Inter-group evaluations were performed using analysis of variance (ANOVA) and Tukey post hoc test. p <0.05 values were deemed significant.

RESULTS

Results of isolated organ bath experiments demonstrated that carbachol-induced contractions dose-dependently relaxed by isoproterenol (10^{-8} to 3.10^{-4} M) in mice detrusor strips obtained from the second-generation antipsychotic drug ziprasidone treated groups shown in Figure 1. However, ziprasidone treatment did not affect KCl responses of mice bladder.

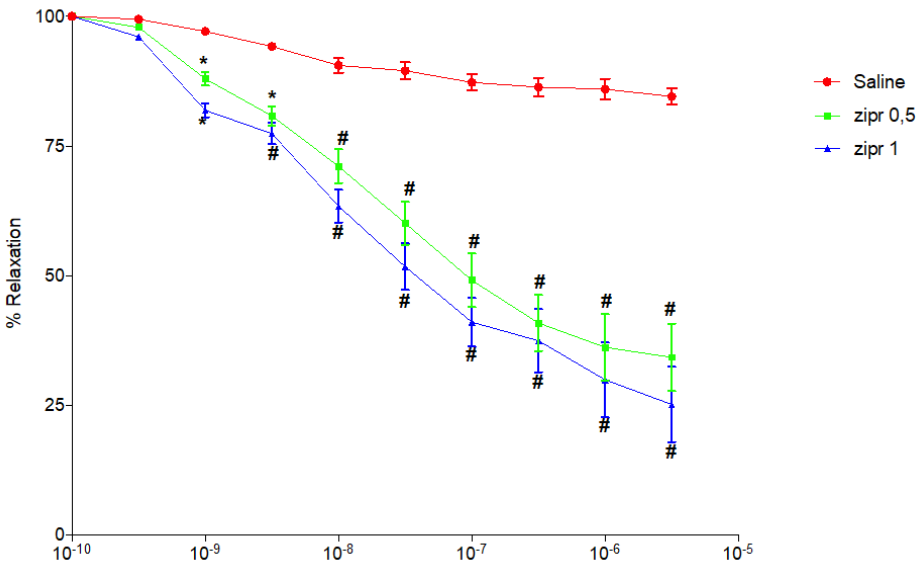

Figure 1. Carbachol-induced contractions dose dependently relaxed by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drug zipr (ziprasidone). Data are presented as mean ± SEM. Significance differences were found at *p <0.05, and #p < 0.01.

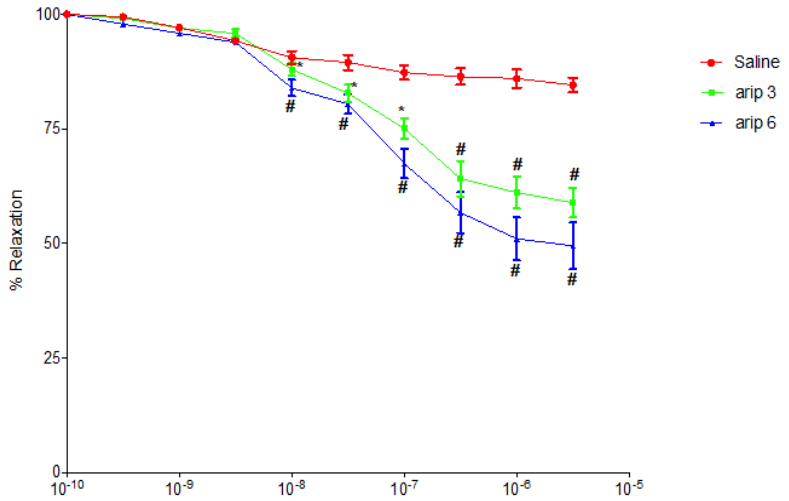

Figure 2. Carbachol-induced contractions dose dependently relaxed by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drug arip (aripiprazole). Data are presented as mean ± SEM. Significance differences were found at *p <0.05, and #p < 0.01.

The findings of the study clearly showed in Figure 2 that aripiprazole dose-dependently inhibits carbachol -induced contractions in mice detrusor strips with isoproterenol (10^{-8} to 3.10^{-4} M). But there were no significant differences found that aripiprazole treatment on KCl responses of the mice bladder.

In addition, relaxation responses of the mice detrusor strips of-obtained from blonanserin and cyamemazine are shown in Figure 3 and Figure 4, respectively. In mice, both blonanserin and cyamemazine dose-dependently induced concentration relaxation with isoproterenol (10^{-8} to 3.10^{-4} M). However, blonanserin and cyamemazine treatments had no effect on KCl responses of mice bladder.

We also showed that carbachol-induced contractions significantly don't relax by isoproterenol in mice detrusor strips exposure with drug nemonapride treated group shown in Figure 5. Nemonapride treatment did not affect KCl responses of mice bladder.

In this research, the ranking of their relaxing potencies of the mice detrusor strips was blonanserin > ziprasidone > cyamemazine > aripiprazole.

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

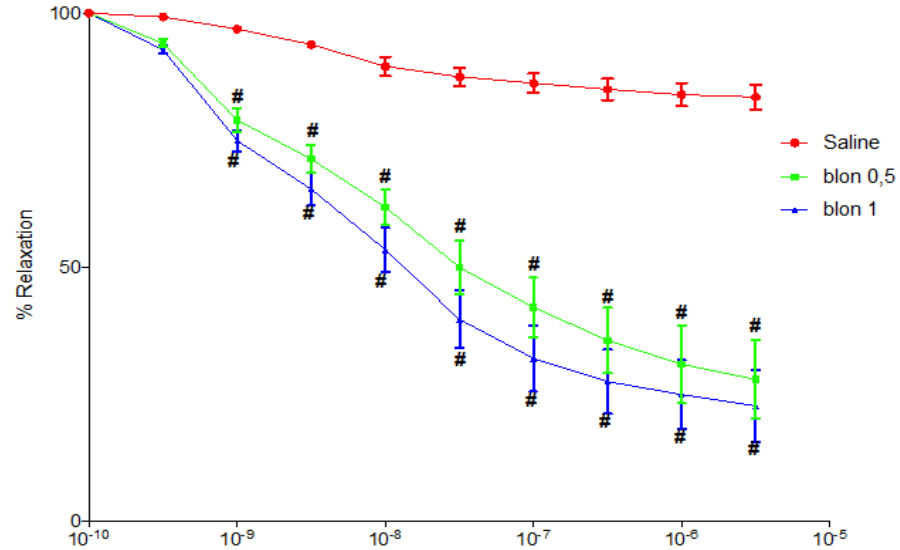

Figure 3. Carbachol-induced contractions dose dependently relaxed by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drug blon (blonanserin). Data are presented as mean ± SEM. Significance differences were found at *p <0.05, and #p < 0.01.

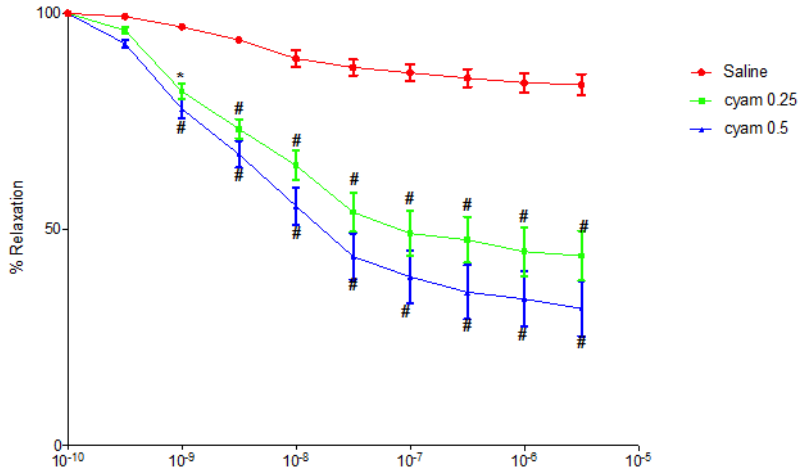

Figure 4. Carbachol-induced contractions dose dependently relaxed by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drug cyam (cyamemazine). Data are presented as mean ± SEM. Significance differences were found at *p <0.05, and #p < 0.01.

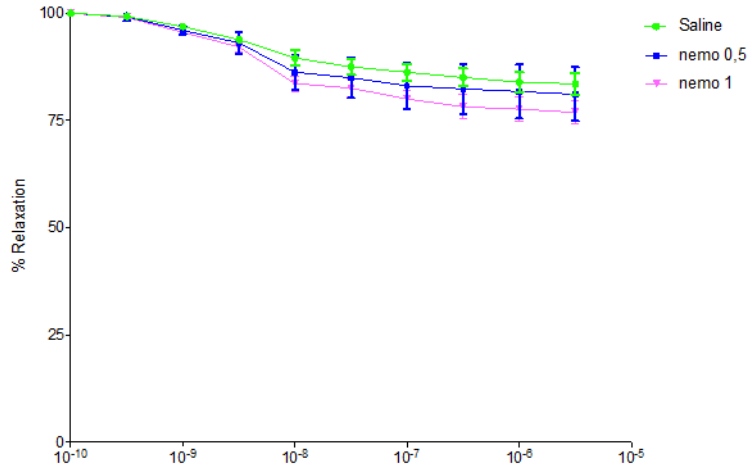

Figure 5. Carbachol-induced contractions don't relax by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drug nemo (nemonapride). Data are presented as mean ± SEM.

DISCUSSION AND CONCLUSION

Micturation is a complex set of events. While micturition is involuntary in the newborn period, it is learned and controlled by the cerebral cortex, in the next period. The coordination of the sphincter and detrusor is provided by the pontin voiding center. Several pathological conditions such as aging, diabetes mellitus, bladder outlet obstruction, spinal cord injury, stroke and brain injury, Parkinson's disease, multiple sclerosis, interstitial cystitis, stress, and depression may lead to the manifestation of overactive bladder (OAB).[19]

Neurological disease is highly associated with lower urinary tract dysfunction, due to impaired regulatory influence of the innervation on the lower urinary tract. The sensory activity involves the understanding of afferent signaling, including signal transduction and afferent traffic, gating, sensitization, and conscious perception.[20] Motor control coordination of urination is done by the pontin urination center.[20] The role of potassium channel subgroups like TREK -1 (KCNK2, K2P2.1), TREK-2 (KCNK2, K2P10.1), and TRAAK (KCNK4, K2P4.1) in detrusor contraction have been investigated. Detrusor overactivity associated with a decrease in functional TREK-1 channels has been demonstrated in an animal model with partial bladder outlet obstruction.[21] It is known that TREK-1 is the main potassium channel in bladder smooth muscle. Increased basal tone and increased spontaneous contractile activity in overactive detrusor specimens indicate that TREK-1 channels affect the bladder filling phase.[22,23] In a recent study, in rats with partial bladder outlet obstruction and secondary overactive detrusor, TREK-1 recep-

tor upregulation was detected in the dorsal root ganglia which reduces the overactive detrusor.[24]

It is known that antipsychotics act through D1, D2, D3, H1, 5-HT2 receptors. Additionally, it is claimed that the effects of some antipsychotics are also mediated by potassium channels. In a study, it has been shown that TREK-1 is the most widespread potassium channel in detrusor.[25] TREK-1 and TREK-2 channels are usually voltage-independent or weakly voltage-dependent and provide the resting membrane potential as a leak-type K+conductance.[26]

Antipsychotic drugs particularly inhibit TREK-1 and due to that effect, they cause relaxation in the detrusor.[24] Although urinary retention has been observed as a result of the use of antipsychotic drugs, their effects on bladder smooth muscle contractions have not been investigated. 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.[25] We used ziprasidone, aripiprazole, blonanserin, cyamemazine, and nemonapride which are used especially in the treatment of schizophrenia, and we think these drugs may be altered urination functions. In our study, carbachol-induced contractions are dose-dependently relaxed by isoproterenol in mice detrusor strips obtained from second-generation antipsychotic drugs ziprasidone, aripiprazole, blonanserin, and cyamemazine treated group.

Global downregulation of TREK-1 channels has dual effects on detrusor contractility and micturition patterns in vivo. The integrative effects of TREK-1, likely, depending on the expression and function of the channel not only in detrusor myocytes but also in afferent and efferent neural pathways regulating micturition. It is known that potassium channels play a role in smooth muscle relaxation.[27] The drugs we use may act on central and/or peripheral receptors. These drugs may also act through potassium channels (TREK).

In the central nervous system, dopaminergic pathways exert inhibitory and excitatory effects on the micturition reflex through D1-like (D1 or D5 subtypes) and D2-like (D2, D3, or D4 subtypes) dopaminergic receptors, respectively. In anesthetized cats, activation of dopaminergic neurons in substantia nigra has been shown to inhibit bladder contractions via D1-like receptors. In a study, a D1 dopaminergic antagonist facilitated the micturition reflex whereas a D1 agonist (SKF 38393) didn't alter reflex bladder contractions in awake rats, suggesting that D1 receptor-mediated suppression of bladder activity is tonically active in the normal awake state.[28]

Conversely, activation of central D2-like dopaminergic receptors with bromocriptine facilitated the voiding reflex pathway in rats, cats, and monkeys. D2-like receptor-mediated facilitation of the micturition reflex may involve actions on the spinal cord as well as actions on the brain stem because microinjection of quinpirole intrathecally in rats or dopamine into the PMC in cats reduces bladder capacity and facilitates the micturition reflex.[22] Chronic use of these drugs is likely to cause adaptive changes in the bladder. It is also likely to have some effects through presynaptic hetero-receptors at autonomic neuroeffector junctions in the bladder.

In conclusion, we used second-generation antipsychotic drugs such as ziprasidone, aripiprazole, blonanserin, cyamemazine, and nemonapride. These antipsychotic drugs increased the isoproterenol-induced relaxations of the detrusor smooth muscle that increased the bladder capasity. We found that these drugs cause relaxation in the bladder muscle. We think that these effects of drugs mainly act 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 develop drugs for overactive bladder in the future.

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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