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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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STIMULATION OF B3-RECEPTOR-INDUCED CENTRAL NEUROGENIC EDEMA AND VITIATED ELECTROLYTE HOMEOSTASIS IN EXPERIMENTAL RODENT MODEL

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Abstract.

Mirabegron is one of the recently introduced treatments for overactive bladder which avoids the undue effects of antimuscarinics such as constipation, headache, and dry mouth. This study investigated chronic relatively high doses of beta3 adrenergic receptor activation effect on electrolyte hemostasis and possible consequence on the central nervous system viability. In the present study, serum sodium, potassium, chloride, and calcium ion levels using flame photometry had been measured and eosin and hematoxylin staining for cerebral vasculature in the brain striatum. Results showed that chronic administration of mirabegron has a modest decrease in sodium, chloride, and potassium levels while increasing calcium serum levels. Moreover, edema and neuronal degeneration have been observed in Wistar rats. In summary, a chronic high dose of beta 3 adrenergic agonist Mirabegron might have a deleterious effect on electrolytes in question homeostasis due to loss of selectivity to beta 3 adrenoceptor when administered in a high dose.

Key words. Sodium, potassium, chloride, calcium, mirabegron, B3-adrenoreceptor.

Introduction.

Worldwide prevalence of lower urinary tract symptoms, overactive bladder (OAB), and urinary incontinence are high, and the numbers of affected people tend to increase with time approximately 4.3 billion, especially in developing regions [1]. The incidence of urgent urinary incontinence related to OAB is approximately 10 in women and 14% in men which makes it one of the most encountered complaints worldwide [2]. the latter causing great social and economic burdens on both individuals and families. In severe cases, it causes a great deal of distress and embarrassment [3,4]. Mirabegron is the first clinically used selective beta-3 adrenergic receptor agonist which is approved to treat OAB symptoms [5,6]. Overactive bladder is defined as urgency, with or without urgency urinary incontinence, with increased daytime frequency and nocturia [7]. these symptoms are indicators of urodynamically detrusor overactivity. However, it can be due to other factors causing ureterovesical dysfunction [8,9]. The distribution of functional beta-adrenoceptors (1, 2, and 3) was reported by Tyagi et. al. in the urothelium and detrusor muscle of the human bladder which revealed that selective beta3 adrenoceptor agonist solabegron evoked a significant concentration-dependent relaxation of the isolated bladder trips. These findings suggested the selective beta3 adrenoceptor agonist as a potential novel treatment for OBD [10]. Mirabegron has unique mechanisms of action to treat OBD by stimulating the beta-3 adrenergic receptor by doing so it increases voiding intervals through increases the compliance of the urinary bladder by detrusor urinary bladder smooth muscle relaxation which in turn increases urinary bladder accommodation to larger urine volume without urination urgency [11-15]. In addition, Mirabegron has been suggested to treat several other clinical conditions like erectile dysfunction related to lower urinary tract symptoms /benign prostatic obstruction patients by clinical report however, the mechanism of action in this clinical situation was not illustrated clearly [16] Mirabegron is considered a new advance in the treatment of OAB symptoms cause the commonly used treatment was antimuscarinic agents causing troublesome adverse effects, for instance, dry mouth, confusion, constipation, headache, and glaucoma [17,18], and although other treatments for has been proposed to treat OAB symptoms like tramadol, gabapentin and botulinum toxin [19-21], however, antimuscarinic had considered being the mainstay of treatment for OAB for decades. The safety and tolerability of mirabegron draw great attention. Clinical safety was reported by Nitti V W et. al. through pooling data from three randomized, placebo-controlled, double-blind, and over 12 weeks of three different mirabegron doses (25,50, and100mg daily) which revealed that mirabegron treatment was associated with main hypertension, nasopharyngitis, and even urinary tract infection among other less incident adverse events [22,23]. As part of phase four studies, a multicenter, randomized, double-blind, placebo-controlled, parallel comparison clinical study investigated the efficacy and safety profile of mirabegron, which revealed that mirabegron reduces OAB symptoms in men after 12 weeks of treatment [24]. Also, a recent clinical study showed the efficacy of 50 mg of mirabegron in improving women suffering from OAB and urgency urinary incontinence or mixed urinary incontinence versus placebo including micturition frequency, and urinary incontinence [25]. Several studies have investigated the impact of mirabegron on different body organs and functions for instance female sexual function and the possible cognitive adverse effects and high incidence of headache and migraine [26-28]. Philip et al. have reported that elevation of potassium chloride has stimulatory effects on bladder detrusor smooth muscle. The latter finding can be one of the mechanisms of action that can control OAB [29]. Activation of beta-3 adrenergic receptor has intriguing effects on mineral homeostasis which might have a role in its effect on bladder detrusor smooth muscle. This study aims to investigate whether Mirabegron's mechanisms of action could include its effect on the homeostasis of sodium, potassium, and/or calcium.

The aims of this study are the investigation of the possible adverse effect of continuous stimulation of beta 3 adrenoceptors on brain tissue morphology and electrolyte hemostasis.

Materials and methods.

Animals: Randomly chosen ten male Wistar rats aged between 3-4 months were used in the current study. All animals were kept under a controlled environment at a temperature 23-25°C and humidity of 50-55%. All animals had access to food and water ad libitum. All the protocols and procedures had been approved by Ninevah university [30-32].

Ten rats were divided into two groups, first group was administered 6 mg/kg of mirabegron while the second group was administered tap water orally once daily for three months.

Biochemical analysis: Blood samples of five rats from each group were exsanguinated by Retro orbital blood withdrawal. The serum was separated by centrifugation 1000g after lifting the blood sample at from temperature for 30-60min Electrolytes analysis of Sodium, potassium, and calcium concentrations in serum were measured by flame photometry Instrumentation Laboratory, Lexington, MA.

Histological study: Rat's brains were kept in paraformaldehyde 10% in phosphate saline buffer overnight for fixation then embedded in paraffin for sectioning and stained with Hematoxylin-eosin.

Statistical analysis: An unpaired t-test was performed to compare between mirabegron group and the control group, using GraphPad Instant software for tabulation. A P value of <0.05 was considered statistically significant.

Results.

Three months of mirabegron 6 mg/kg orally once daily significantly decreases serum sodium and chloride level (P<0.5) in comparison with the control group. Potassium levels also significantly decreased in mirabegron in comparison with the control group. While calcium level significantly elevated with mirabegron use (figure 1).

Rat's brain which was treated for three months with Mirabegron sections showed signs of necrosis and neuronal degeneration (figure 2) under the light microscope.

Discussion.

The current study showed that three months of treatment of rats with 6 mg/kg of mirabegron caused a decrease in both sodium and potassium levels and an increase in calcium levels.

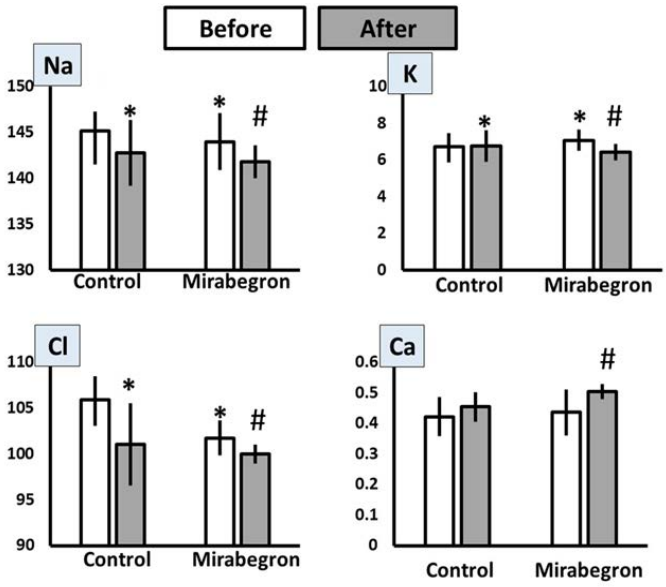

Figure 1. *Disturbances of electrolyte homeostasis (Na, K, Cl, and Ca) stimulation of B3 receptor. Data expressed as mean±SD, *p<0.05 as compared to after stimulation of B3 receptor or control group.*

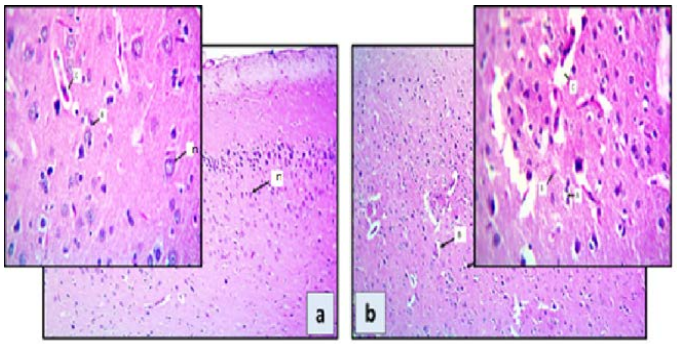

Figure 2. *Representative image for Brain (a) control, (b) after 3-month stimulation of B3 receptor with Mirabegron. H and E stain, 100X and 400X.*

Moreover, 6mg/kg of mirabegron for three months, caused neuronal degeneration and edema.

Beta 3 adrenoceptor is one of the adrenergic receptors activated by catecholamines. Beta adrenoceptor activation is through beta-adrenoceptor-adenylyl cyclase-protein kinase A cascade. Beta 3 adrenoceptors consist of seven membrane-spanning domains consisting of three intra and three extracellular loops plus one extracellular and one intracellular terminal [33]. Beta 3 adrenoceptor is present mainly in the bladder detrusor muscle and in adipose tissue [34].

Mirabegron has drawn a great deal of attention recently because of its unique mechanism of action by direct blocking beta 3 adrenoceptor in the detrusor muscle treating over-active bladder of both neurogenic and non-neurogenic origin. Recently, Mirabegron has been suggested to treat obesity in relatively high doses through an increase in energy expenditure without an increase in blood pressure or heart rate (avoiding cardiovascular undesirable effect) through besieging of white adipose tissue to brown adipose tissue when given in doses of 50 and 100 mg daily while 150 and 200 mg caused cardiovascular adverse effect [35,36].

Zhang and his coworker reported functional pain syndromes and brain damage associated with increased catecholamine activity as they report that continuous activation of beta 2 and beta 3 adrenoceptors for 14 days results in pain at several body regions through the release of pro-inflammatory cytokine tumor necrosis factor-alpha [37]. Consistently, another study by Kline revealed the attenuation of catechol-O-methyltransferase activity can lead to enhanced chronic pain perception in humans, and this pain perception is mediated by beta-adrenoceptors [38]. Functional pain and comorbid depression due to the Catechol-O-methyltransferase enzyme which is responsible for catecholamines metabolism polymorphism has been investigated and the results shown blocking COMT enzyme caused pain and depressive-like behavior was prominent in females who administered COMT inhibitor OR486 continuously over 14 days in addition to increase glucocorticoid receptor expression a well-know stress related receptor [39].

Mild activation of beta2 adrenoceptor can lead to an intracellular influx of potassium causing hypokalemia which in turn decreases the reactivity of detrusor muscle [40-42]. The latter might be one of the suggested mechanisms through which mirabegron can treat OAB. Calcium elevation in this study is not

clear and these action could increase the chance of application of mirabegron for musculoskeletal delimma including spinal injury [43].

Conclusion.

The current study highlights the possible central nervous system adverse effect of mirabegron when used in relatively high doses over an extended time for the first time. The latter effect might be due to the beta 2 or 1 adrenoceptor not being excluded and whether these effects due to electrolytes disturbance could be a marker for these neurological adverse effects need more studies.

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