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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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 and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) 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.

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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.

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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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ANTINOCICEPTIVE TOLERANCE TO CANNABINOIDS IN ADULT MALE MICE: A PILOT STUDY

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The *Cannabis sativa* plant has been used for medicinal purposes for thousands of years by different cultures. The first documentation of cannabis as a medicine appeared in China 5000 years ago when it was recommended for malaria, constipation, rheumatic pains and, mixed with wine, as a surgical analgesic. In India, more than 1000 years BC, the plant was used for various functions, such as a hypnotic and a tranquilizer in the treatment of anxiety, mania and hysteria [19]. The Assyrians inhaled cannabis to relieve symptoms of depression. A Greek physician, Pedacius Dioscorides, between 50 and 70 AD classified different plants, including *C. sativa*, and described the benefits derived from its use in his book *De Materia Medica* [30]. Cannabis was introduced into Western medicine in the 19th century for its analgesic, anti-inflammatory, anti-emetic and anticonvulsant properties.

In the early 20th century, cannabis extracts were used for the treatment of psychiatric disorders, and were especially utilized as sedatives and hypnotics. After the 1930s, medical use of cannabis significantly decreased as it was considered to be an illegal substance, and its use in psychiatry was limited. However, after the identification of the main components of cannabis and the discovery that the endocannabinoid system (ECS) is able to modulate different processes in pain medicine and psychiatric disorders, interest in the use of cannabinoids has been renewed [10,12,13,18,26]. The medical use of cannabis extracts was approved in June 2010 by ten European countries [7].

In the past two decades, numerous tools to perturb the ECS have been developed and demonstrated its potential efficacy for pain relief and in treatment of neurological disorders. However, global targeting of the ECS is also associated with undesirable results, including deleterious effects on memory, cognition, mood, and the development of tolerance and dependence in humans [5,15,27,25,37]. Similarly, laboratory animals also exhibit both tolerance and dependence subsequent to the chronic administration of cannabinoids [2,15,20,29].

Cannabinoids are classified based on their origin into three categories: endocannabinoids (present endogenously in human tissues), phytocannabinoids (plant-derived), and synthetic cannabinoids (pharmaceuticals). Cannabinoids exert an analgesic effect, peculiarly in hyperalgesic conditions associated with neuropathic and inflammatory pain [22]. Components of the cannabinoid system are expressed almost ubiquitously throughout nociceptive pathways, and thus targeting the system via exogenous cannabinoid ligands, or enhancement of endogenous communication can modulate nociceptive signaling at multiple sites including the periphery, dorsal horn of the spinal cord, and supraspinal structures associated with pain processing [31,32,37].

The first cannabinoids to be chemically characterized, delta-***9***-tetrahydrocannabinol (THC), and cannabidiol (CBD) were the most abundant members of this class of natural products in the dried and heated flowers of *C. sativa* varieties that are used for the production of marijuana and hemp, respectively [24]. Accordingly, THC is responsible for the psychoactive effects of marijuana whereas CBD was found to be non-psychotropic [6,20]. Initially, research on cannabinoid acids received little attention, but cannabinolic acid (CBNA), like CBD, has recently been reported to have anti-nausea and anti-anxiety activity and to reduce depressive-like behavior in two genetic animal models of depression [24]. CBNA, a non-psychoactive cannabinoid is formed during storage and aging of plant samples by degradation of tetrahydrocannabinolic acid (THCA), a major component of cannabis resin [3]. Nevertheless, the potential clinical uses of cannabinoids remain strongly limited by the unacceptable adverse effects of cannabis including its psychotropic action [1,13] or tolerance, dependence, and withdrawal symptoms upon drug cessation [15,28,33].

Cannabinoid-based medications possess unique multimodal analgesic mechanisms of action, modulating diverse pain targets in the nervous system. However, more clinical and preclinical studies are needed to address the issues of the tolerance and dependence associated with cannabinoids. Characterizing and modifying drug tolerance is important in the development of and optimization of analgesics in order to relieve pain with repeated use. Some behavioral tolerance effects of cannabinoids have been reported in rodents. For example, tolerance to various effects of THC and synthetic cannabinoid agonists (WIN 55,212-2, CP 55,940) develops readily upon repeated drug administration, and the development of tolerance may depend on sex differences. For example, female rats developed more antinociceptive tolerance to THC than males [34,35].

Because most previous studies examined antinociceptive tolerance to cannabinoids in rats, the present study examined the development of antinociceptive tolerance to repeated administration of THC and CBNA in mice.

Material and methods. Studies were conducted in male mice weighing 30-50 g that were bred at the vivarium of the BMC. The mice were housed under standard conditions (22±2°C, 65% humidity, light from 7:00 a.m. to 8:00 p.m.), and maintained with food and water freely available. Training sessions were carried out five days per week during the daylight hours. Throughout the experiments, animals were treated in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Academy of Sciences, 2003) and all experimental protocols were approved by the local Bioethics Committee of the BMC. We adhered to the Guidelines of the International Association for the Study of Pain regarding investigations of experimental pain in conscious animals [38].

Drugs. Delta-9-THC (250 µg/kg**,** Cerilliant, Sigma-Aldrich) and CBNA (2.5 mg/kg, Cerilliant, Sigma-Aldrich) (in a volume 0.03-0.05 ml) or the same volume of vehicle (10% DMSO (Sigma) in saline) were injected intraperitoneally (i.p.). For studies of tolerance, these drugs were administered repeatedly over five consecutive days (Monday–Friday). Concentrations and volumes of drugs were calculated according to corresponding data in rats [8,35].

Behavioral measures of nociception. Experiments were conducted using three behavioral plantar nociceptive tests: thermal paw withdrawal test (Hargreaves method) (#390, IITC Life Science, Inc., Woodland Hills, CA, USA), mechanical paw withdrawal test using with IITC Electronic von Frey (#3900 rigid tip 90 g range), and Hot Plate Analgesia Meter (#39, IITC).

Thermal paw withdrawal (Hargreaves) test: Mice were first habituated over three successive daily sessions to stand on a glass surface heated to 30±1 ℃ within a ventilated Plexiglass enclosure. Before formal testing, baseline latencies for paw withdrawals evoked by radiant thermal stimulation were measured three times/paw, with at least 5 min elapsing between tests per each paw. A light beam was focused onto the plantar surface of the hindpaw through the glass plate from below, and the latency from the onset of light application to brisk withdrawal of the stimulated paw was measured. To prevent potential tissue damage, a cutoff time of 20 s was imposed if no paw movement occurred.

Mechanical paw withdrawal threshold (von Frey) test: Mice were placed on a mesh stand (#410, IITC) inside plexiglass enclosures and trained for three consecutive daily sessions to acclimate them to the testing environment. The electronic von Frey device registered the force (g) at the moment that the

hindpaw was withdrawn from the semi flexible polypropylene filament. Prior to testing, each paw was tested for baseline mechanical withdrawals at least three times, with a minimum of 5 min between successive measurements per each paw.

Hot plate test: For the hot plate (HP) test, mice were habituated to the testing environment for three successive daily sessions. Mice were placed on an anodized aluminum plate (275mm × 263mm × 15mm) supplied with a Plexiglass enclosure. The plate was heated to 55°C and the latency to the first hindpaw lick or time to first jump was determined. The cut-off time was 20 s for HP latencies.

Behavioral testing. Mice were randomly divided into experimental and control groups. Prior to testing, baseline values for thermal and mechanical tests were assessed. Baseline values were defined as the mean of three measurements for the left and right hindpaws, with 5 min intervals between tests. Each animal was tested with these three tests in the same session. Similar procedures were followed for the repeated microinjection of THC (250 μg/kg) and CBNA (2.5 mg/kg) for four consecutive days. Mice were tested 15 min after drug administration.

All data are presented as mean ± SEM. Paw withdrawal latencies to heat and mechanical paw withdrawal thresholds were compared using One-way analysis of variance with repeated measures (rMANOVA). Post-hoc comparisons between vehicle-treated and THC- or CBNA-treated mice were made using the Tukey-Kramer or Dunnett's multiple comparison tests. The statistical software utilized was InStat 3.05 (GraphPad Software, USA). Differences between groups of mice were considered statistically significant if $P<0.05$.

Results and discussion. In this first series of experiments, we studied whether tolerance would develop in mice following systemic (i.p.) administration of 250 μg/kg THC. Our results showed that THC induced strong antinociception in all three behavioral tests on the first day of the experiment (Fig. 1). The latency of thermal paw withdrawal (Hargreaves test) was significantly increased during five days of testing, [rMANOVA: $F(16,55)=150.85$, $P<0.0001$, $n=12$]. Dunnett's comparison post hoc test between baseline control and experimental data clearly showed significant increases in thermal withdrawal latency for the first ($t=23.699$, $p<0.01$), the second ($t=15.985$, $p<0.01$), the third ($t=12.329$, $p<0.01$), the fourth ($t=7.179$, $p<0.01$), and the fifth days ($t=3.156$, $p<0.05$) (Fig. 1A). As can be seen from this Fig., from the second day of testing the latency of the reflex is progressively reduced, indicating the development of tolerance to repeated systemic administration of THC.

We obtained similar results for the hot plate test [rMANOVA: $F(10,25)=23.596$, $P<0.0001$, $n=6$]. In this test, withdrawal latency was significantly increased in the first three days of the experiment, on

the first ($t=7.475$, $p<0.01$), second ($t=4.377$, $p<0.01$) and third days ($t=2.710$, $p<0.05$). However, antinociception was gradually reduced over the five experimental days (Fig. 1B). Mechanical paw withdrawal thresholds (von Frey test) also increased after THC [rMANOVA: $F(16,55)=63.725$, $P<0.0001$, $n=12$]. The Dunnett post hoc test confirmed this effect on the first ($t=14.505$, $p<0.01$), second ($t=10.177$, $p<0.01$), third ($t=6.464$, $p<0.01$) and fourth days ($t=2.938$, $p<0.05$). As for the antinociceptive effects on withdrawal responses to heat, tolerance to THC was evident (Fig. 1C).

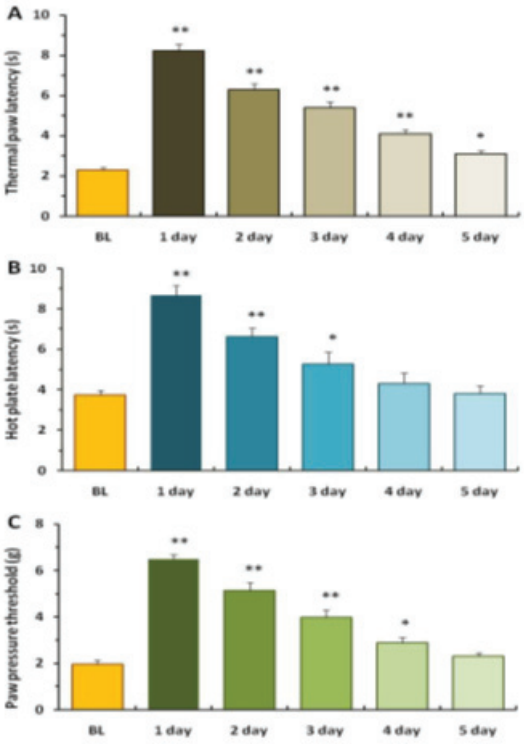

Fig. 1. Antinociceptive tolerance to systemic injections of THC. Latency of thermal paw withdrawal on the Hargreaves test (A), latency of paw withdrawal on the hot plate (B), and mechanical withdrawal threshold (von Frey test) (C) increased after THC. It is noteworthy that as a result of repeated injections of THC over a period of five days, there is a progressive reduction in withdrawal latencies and thresholds indicating development of tolerance

In the second series of experiments, we explored the second cannabinoid – cannabinolic acid (CBNA), which, unlike THC, has no psychotropic action. Systemic (i.p.) administration of CBNA (2.5 mg/kg) produced stronger antinociception and, to some extent, more rapidly developed tolerance than THC. In all these three behavioral tests, rMANOVA showed a significant increase in withdrawal responses to thermal (Hargreaves), [$F(16,55)=49.245$, $P<0.0001$, $n=12$], and hot plate [$F(10,25)=56.47$, $P<0.0001$, $n=6$], and mechanical stimuli (von Frey) [$F(16.55)=142.07$, $P<0.0001$, $n=12$].

Dunnett's post hoc test on paw thermal stimulus revealed a significant increase in withdrawal latency on the first ($t=12.452$, $p<0.01$), second ($t=8.505$, $p<0.01$) and third ($t=3.949$, $p<0.01$) days (Fig. 2A). A similar increase in latency was observed with

the hot plate test during the first three days (t=13.324, p<0.01, 1st day), (t=6.917, p<0.01, 2nd day), and (t=3.910, p<0.01, 3rd day) (Fig. 2B). Mechanical withdrawal thresholds test also showed a significant increase on the first (t=23.208, p<0.01), second (t=11.542, p<0.01), third (t=7.118, p<0.01) and fourth days (t=3.029, p<0.05) (Fig. 2C).

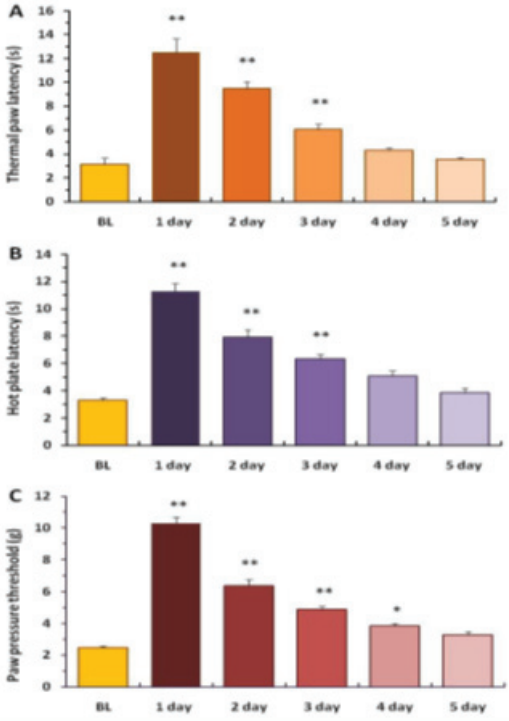

Fig. 2. Antinociceptive tolerance to systemic injections of CBNA. Latencies of thermal paw withdrawal using the Hargreaves test (A), and the hot plate test (B), and mechanical withdrawal thresholds (von Frey test) (C) increased after CBNA. Repeated administration of CBNA over a period of five days resulted in a progressive reduction in the antinociceptive effects of CBNA, indicating the development of analgesic tolerance

Fig. 2 clearly shows that repeated i.p. administration of CBNA resulted in a gradual decrease in the antinociception in of the behavioral measures. Withdrawal responses to heat and to mechanical stimuli returned to baseline by the 4th and 5th day of testing, respectively. Thus, as for THC, tolerance developed following repeated administration of CBNA.

Our results showed that while the two major components of cannabis, THC and CBNA, produced potent antinociception to heat and mechanical stimuli in mice, repeated systemic administration of them resulted in rapid tolerance. Indeed, within 4-5 days of administration, withdrawal responses returned to baseline values. It has been found that chronic treatment of rodents with THC results in tolerance to its acute behavioral effects, such as analgesia, motor inhibition, and the memory-disruptive effects of cannabis. Such tolerance depends on dose, duration of treatment, species, and the dependent variable measured, and there is significant consensus that the mechanism of such tolerance is pharmacodynamic and not pharmacokinetic [14]. Recent functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) studies in humans showed that an understanding of the pharmacodynamic mechanism for the development of tolerance to cannabis is needed in the context of the long-term therapeutic use of cannabis-based medications [17].

Evidence suggests that the effects of acute administration of THC are less prominent in individuals with a regular pattern of cannabis use compared to non-regular users. These studies indicate that frequent cannabis users report impairments in a broad range of cognitive functions upon acute THC administration. In this regard, cognitive functions in humans (sustained attention, psychomotor ability, distractibility, verbal learning, etc.) appear to be the domain most likely to demonstrate tolerance upon repeated exposure, with some evidence of full tolerance indicating a complete absence of an acute effect [4].

The adverse effects of repeated THC administration may occur through a combination of pathways involving cannabinoid receptor activation, accumulation of cannabinoids and their metabolites, and upregulation of neuroinflammatory cytokines. Thus, tolerance may play a relevant role in the cascade of neurobiological events leading to disorders affecting brain chemistry and circuitry [4]. We suggest that this possibility should be taken into account when prescribing cannabis medications for pain therapy.

Numerous studies have demonstrated that: (i) cannabinoids suppress nociceptive processing, (ii) this suppression involves supraspinal, spinal and peripheral mechanisms, (iii) endogenous cannabinoids suppress pain, (iv) cannabinoids suppress neuronal hyperexcitability and central sensitization, (v) cannabinoids suppress hyperalgesia and allodynia through actions at CB1 and CB2 receptors, and finally (vi) cannabinoid receptors are anatomically localized to modulate nociceptive transmission through actions in the periphery and spinal cord [2,11,16,22,28]. Thus, cannabinoids may be used as an alternative to opioids or as an adjunct medication to reduce the doses of opioids required for analgesia.

There are multiple mechanisms by which cannabinoids produce antinociception. Morphological and physiological evidence suggest that cannabinoids produce antinociception by decreasing sensitization of primary afferent nociceptors and through a presynaptic CB1R-mediated modulation of nociceptive input to the spinal cord [2,21,29]. The attenuation of capsaicin-induced increase in excitability and depolarization of the substantia gelatinosa cells suggests that the strong inhibitory effect of the cannabinoids is capable of reducing the nociceptive input to the spinal dorsal horn [21,29]. This strong inhibitory effect is likely to be one of the mechanisms of the antihyperalgesic and analgesic effects of cannabinoids in various animal models of acute and chronic pain [21,29,33].

In the brain, low levels of cannabinoid receptors in brainstem regions that control vital heart rate and respiratory function provide an anatomical basis for the low toxicity of cannabinoids. However, the psycho-activity of direct acting CB1R agonists proved to be a major barrier to their use as therapeutic tools in the pharmacotherapy for chronic pain. More encouraging results have arisen from a number of studies showing positive effects of CB2R agonists, locally administered cannabinoids, inhibitors of the anandamide-degrading enzyme or the putative anandamide transporter, or the use of new atypical cannabinoids. Such novel targets for pain pharmacotherapy represent important future directions for research in this field [22,36].

Concerning the molecular mechanisms of antinociceptive tolerance, it has been recently discovered that c-Jun N-terminal kinase (JNK) signaling pathways delay tolerance to the antinociceptive and anti-allodynic effects of THC, but not to synthetic cannabinoid agonists (CP55,940 and WIN55,212-2) in wild-type mice using the formalin test and in mice with cisplatin-evoked neuropathic pain using the tail-flick assays. These results emphasize the agonist-specific mechanism of cannabinoid tolerance [9].

Further studies are needed to better understand the neuronal and molecular mechanisms underlying the development of tolerance upon repeated cannabinoid exposure regarding agonist-induced downregulation of cannabinoid receptors and their intracellular trafficking. Such information is required in order to optimally develop effective cannabinoid agonists that lack antinociceptive tolerance.

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SUMMARY

ANTINOCICEPTIVE TOLERANCE TO CANNABINOIDS IN ADULT MALE MICE: A PILOT STUDY

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Over the past two decades, numerous tools have been developed to study the endocannabinoid system. Studies show the potential effectiveness of endocannabinoids for the relief of pain and neurological disorders. However, global targeting of the endocannabinoid system has also been associated with unwanted outcomes, including deleterious effects on cognitive and emotional functions, the development of tolerance and dependence, and withdrawal symptoms after drug cessation in humans. The main objective of the present study was to determine whether male mice develop tolerance to delta-9-tetrahydro-cannabinol (THC) and cannabinolic acid (CBNA)-induced antinociception with long-term treatment. Using behavioral tests of mechanical and thermal nociception, we found that systemic (intraperitoneal, i.p.) administration of THC and CBNA resulted in strong antinociception on the first day of the experiment. However, over the next four days, the behavior indices of antinociception to mechanical and thermal stimuli gradually decreased, indicating the development of tolerance following systemic administration of these drugs. Thus, the two main components of cannabis, THC and CBNA, are characterized by the development of tolerance in mice as a result of their repeated i.p. administration.

Keywords: allodynia, analgesia, hyperalgesia, nociception, pain, withdrawal reflexes.

РЕЗЮМЕ

АНТИНОЦИЦЕПТИВНАЯ ТОЛЕРАНТНОСТЬ К КАННАБИНОИДАМ У ВЗРОСЛЫХ МЫШЕЙ-САМЦОВ: ПРЕДВАРИТЕЛЬНОЕ ИССЛЕДОВАНИЕ

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За последние два десятилетия разработано множество подходов для изучения эндоканнабиноидной системы. Исследования показывают потенциальную эффективность эндоканнабиноидов для облегчения боли и неврологических расстройств. Однако глобальное нацеливание на эндоканнабиноидную систему также связано с нежелательными последствиями, включая угнетающее воздействие на когнитивные и эмоциональные функции, развитие толерантности и зависимости, а также симптомы отмены.

Цель исследования - определить, развиваются ли у самцов мышей толерантность к дельта-9-тетрагидроканнабинолу (THC)- и каннабиноловой кислотой (CBNA)-индуцированной антиноцицепции при длительном лечении.

Используя поведенческие тесты механической и температурной ноцицепции, обнаружено, что системное (внутрибрюшинное) введение THC и CBNA приводит к сильной антиноцицепции в первый день эксперимента. Однако в течение следующих четырех дней показатели поведения, связанные с антиноцицепцией к механическим и тепловым раздражителям, постепенно снижались, указывая на развитие толерантности после системного введения этих препаратов.

Таким образом, два основных компонента каннабиса, THC и CBNA характеризуются развитием толерантности у мышей в результате их повторного внутрибрюшинного введения.

რეზიუმე

ზრდასრულ მამრ თაგვებში კანაბინოიდებისადმი განვითარებული ანტინოციცეპტიკური ტოლერანტობა: წინასწარი კვლევა

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[1]ივ. ბერიტაშვილის ექსპერიმენტული ბიომედიცინის ცენტრი, ტკივილისა და ანალგეზიის ლაბორატორია, თბილისი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ფიზიოლოგიის დეპარტამენტი, საქართველო; [3]მინესოტას უნივერსიტეტი, დიაგნოსტიკური და ბიოლოგიური მეცნიერებების დეპარტამენტი, მინეაპოლისი, მინესოტა, აშშ

ბოლო ორი ათწლეულის განმავლობაში შემუშავდა მრავალი მიდგომა ენდოკანაბინოიდური სისტემის შესასწავლად. რიგმა კვლევებმა უჩვენეს ენდოკანა-

ბინოიდების პოტენციური ეფექტურობა ტკივილისა და ნევროლოგიური დარღვევების შემსუბუქებაში. თუმცა, ენდოკანაბინოიდური სისტემის მონაწილეობა ასევე ასოცირდება არასასურველ გვერდით მოვლენებთან, მათ შორის აღსანიშნავია შემეცნებითი და ემოციური ფუნქციების დათრგუნვა, ტოლერანტობისა და დამოკიდებულების განვითარება და პრეპარატის მოხსნის სინდრომი.

კვლევის მიზანი იყო იმის დადგენა, განუვითარდებოდათ თუ არა მამრ თაგვებს ტოლერანტობა დელტა-9-ტეტრაჰიდროკანაბინოლითა (THC)- და კანაბინოლის მჟავით (CBNA)-ინდუცირებული ანტინოციცეფციის მიმართ.

მექანიკური და ტემპერატურის ქცევითი ტესტების გამოყენებით გამოვლინდა, რომ THC და CBNA სისტემურ (ინტრაპერიტონეალური) შეყვანამ გამოიწვია ძლიერი ანტინოციცეფცია ექსპერიმენტის პირველ დღეს. თუმცა, მომდევნო ოთხი დღის განმავლობაში ქცევითი მაჩვენებლები, რომლებიც დაკავშირებულია მექანიკურ და თერმულ სტიმულებთან, თანდათან დაქვეითდა, რაც მიუთითებს ტოლერანტობის განვითარებაზე ამ პრეპარატების მიმართ.

ამრიგად, კანაფის ორი ძირითადი კომპონენტი, THC და CBNA, ხასიათდება თაგვებში ტოლერანტობის განვითარებით მათი განმეორებითი ინტრაპერიტონეალური ინიექციებისას.

Na, K-ATPase AND Cl-ATPase REGULATION BY DOPAMINE

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The neurotransmitter (NT)-dependent regulatory system of Na, K-ATPase, and Cl-ATPase have been discovered in the synaptic membranes of the rat brain. This regulation is implemented with noradrenaline (NA), dopamine (DA), serotonin (5HT), and acetylcholine (ACh). The action of NA, DA, and 5HT, in turn, is regulated by the factor found in the synaptosomal cytosol fraction (SFa). The addition of SFa abolishes Na, K-ATPase inhibition induced by the action of the above-mentioned NTs, leading to the enzyme activation [9,6].

Regulation of the Cl-ATPase and Na/K-ATPase with an NT and SFa has functional importance because it is specific for the synaptic membranes, while SFa is localized exclusively in the synaptic cytosol. The effect of NT and SFa action on the Na, K-ATPase is characterized by tissue specificity [9,3]. The effect is different in various regions of the brain and different types of synapses [9]. The ratios of activatory/inhibitory mechanisms and their depths at different stages of ontogenesis and in the animals of different habitats vary as well [10]. However, the molecular mechanisms of the NT and SFa action on Cl-ATPase and Na, K-ATPase are yet unknown. Clarification of these mechanisms will provide more information on the functional role of this regulation.

The material presented in this work is an endeavor to elucidate the above problem; we have investigated the action of dopamine on Cl-ATPase and Na, K-ATPase transport stoichiometry.

Material and methods. The synaptic fraction from rat brains served as the Cl-ATPase and Na, K-ATPase preparation, which was collected between the 1.2-0.9 *M* sucrose layers [2]. The protein concentration was evaluated by the Lowry method [14], the inorganic phosphorus by the modified Fiske-Subbarow [4], and the Kazanova-Maslova method [7]. The Na, K-ATPase activity (*V*) was assessed as the ouabain-sensitive part of the total ATPase activity, in μmolP_i h^{-1} *(mg protein)*$^{-1}$.

The standard reaction medium for Na/K-ATPase assay contained: 2 mM ATP, 2 mM $MgCl_2$, 140 mM NaCl, 5 mM KCl and 50 mM Tris-HCl, pH 7,7. Assessment of the Mg-ATPase was conducted in the incubation medium containing 0,2 mM ouabain, 2mM ATP, 2 mM $MgCl_2$, 145 mM KCl, and 50 mM Tris-HCl, pH 7,7. With respect to Mg-ATP, the dissociation constant adopted was 0.085mM [1,10]. For Cl-ATPase reagent medium always contained 30 mM Tris–Malate (pH 7.65), 0.4 mM EGTA, and 0.3 mM ethacrynic acid (the specific inhibitor of Cl-ATPase [5,15]. Cl-ATPase was measured as the difference between Cl^--containing incubation and ethacrynic acid-containing media.

The Cl-ATPase and Na, K-ATPase enzyme systems reaction is a function of many physiological ligand sands. Each one may exert an activating or inhibiting action on the enzyme. To analyze the enzymatic reaction's initial velocity, it is required to get V = f (MgATP, Mg_f^{2+}, ATP_f, Cl^-) function for the Cl-ATPase and V = f (MgATP, Mg_f^{2+}, ATP_f, Na^+, K^+) for the Na, K-ATPase to the one variable function, where the values of other ligands are constant.

In case the conditions are unchanged during the reaction, with the enzyme functional unit structure being stable, the initial velocity would be a one-variable function and would be reflected by the following analytical formula:

$$V = e_0 \frac{x^n \sum_{i=0}^{p} \alpha_i x^i}{\sum_{i=0}^{S} \beta_i x^i} \quad S = n + m + p$$

where α_1 and β_1 are the sum of products of individual velocity coefficients and constant ligands' concentrations. X is a variable ligand concentration; e_0- is the enzyme overall concentration. n, m, and p represent power parameters and are positive integers. n is the number of sites for essential activators, m is the number of