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Analgesic activity of a new cannabinoid CB_1 receptor modulator

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ABSTRACT

Aim. To study the analgesic activity, the effect on motor functions, and the potential ulcerogenic effect of a new 2*H*-chromene derivative, a cannabinoid CB_1 receptor modulator (code name – CHR).

Materials and methods. The analgesic activity of the CHR compound was studied when injected intragastrically at an effective dose of 5 mg / kg in mouse models of acute chemogenic pain (formalin test), acute visceral pain (the acetic acid-induced writhing test), and thermal nociception (hot plate test and tail-flick test). It was compared to the effect of tramadol and morphine or diclofenac sodium at doses of 20.4 or 10 mg / kg, respectively. The effect of a single intragastric injection of the CHR compound at a dose of 5 mg / kg on motor activity was evaluated in the open field test. The potential ulcerogenic effect of the CHR compound at a dose of 5 mg / kg with repeated intragastric administration was compared with the effect of diclofenac sodium at a dose of 10 mg / kg.

Results. With subplantar administration of formalin to mice, the 2*H*-chromene derivative reduced the number of pain reactions by 43–63% ($p < 0.05$). With intraperitoneal administration of acetic acid to mice, it reduced the number of writhing responses by 50% and had the same analgesic effect as diclofenac sodium and tramadol. In the hot plate test, the CHR compound increased the latency time to painful stimuli by 34% ($p < 0.05$). In the tail-flick test, it increased the latency time to painful thermal sensations by 32% ($p < 0.05$). The CHR compound at an effective dose of 5 mg / kg did not change the motor activity of mice in the open field test and did not cause the formation of erosions and ulcers in the gastric mucosa when administered repeatedly to rats.

Conclusion. The 2*H*-chromene derivative CHR at an effective dose of 5 mg / kg has a pronounced analgesic effect in mouse models of chemogenic, visceral, and thermal pain, which is as strong as that of tramadol, morphine, and diclofenac sodium used at effective doses. The CHR compound at an effective dose does not inhibit motor functions and does not have an ulcerogenic effect.

Keywords: 2*H*-chromene derivative, analgesic activity, effect on motor functions, potential ulcerogenic effect, mice, rats

Conflict of interest. The authors declare the absence of obvious and potential conflict of interest related to the publication of this article.

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Анальгетическая активность нового модулятора каннабиноидного CB_1-рецептора

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РЕЗЮМЕ

Цель – изучить анальгетическую активность, влияние на двигательные функции и потенциальное ульцерогенное действие нового производного 2*H*-хромена – модулятора каннабиноидного CB_1-рецептора (шифр – CHR).

Материалы и методы. Анальгетическую активность соединения CHR изучали при введении в желудок мышам в эффективной дозе 5 мг/кг на моделях острой хемогенной боли (формалиновый тест), острой висцеральной боли (тест «уксусные корчи») и термической соматической боли (тесты «горячая пластина» и отдергивание хвоста от теплового излучения) в сравнении с действием трамадола, морфина или диклофенака натрия в дозах 20, 4 или 10 мг/кг соответственно. Влияние на двигательные функции соединения CHR при однократном введении в дозе 5 мг/кг в желудок мышам оценивали в тесте «открытое поле». Потенциальное ульцерогенное влияние соединения CHR в дозе 5 мг/кг при многократном введении в желудок крысам сравнивали с действием диклофенака натрия в дозе 10 мг/кг.

Результаты. В эксперименте с субплантарным введением формалина мышам производное 2H-хромена CHR уменьшало количество болевых реакций на 43–63% ($p < 0,05$). При внутрибрюшинном введении мышам уксусной кислоты оно снижало количество «корчей» на 50% и не уступало анальгетическому эффекту диклофенака натрия и трамадола. В тесте «горячая пластина» соединение CHR увеличивало латентное время до наступления болевой реакции на 34% ($p < 0,05$). В тесте отдергивания хвоста от теплового излучения увеличивало срок до появления термической боли на 32% ($p < 0,05$). Соединение CHR в эффективной дозе 5 мг/кг не изменяло двигательную активность мышей в тесте «открытое поле» и не вызывало образования эрозий и язв в слизистой оболочке желудка при многократном введении крысам.

Заключение. Производное 2*H*-хромена CHR в эффективной дозе 5 мг/кг оказывает выраженное анальгетическое действие при экспериментальной хемогенной, висцеральной и термической боли, по анальгетическому действию не уступает опиоидным анальгетикам трамадолу и морфину и нестероидному противовоспалительному средству диклофенаку натрия, использованным в эффективных дозах. Соединение CHR в эффективной дозе не тормозит двигательные функции и не обладает ульцерогенным влиянием.

Ключевые слова: производное 2*H*-хромена, анальгетическая активность, влияние на двигательные функции, потенциальное ульцерогенное действие, мыши, крысы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено с привлечением собственных средств.

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INTRODUCTION

Cannabinoids are a class of natural and synthetic compounds with a pronounced analgesic effect. They activate CB_1 receptors in spinal ganglia, dorsal horns of the spinal cord, nucleus raphe magnus, periaqueductal gray matter, limbic system, and cerebral cortex [1–3]. When metabotropic presynaptic G_i-protein-coupled CB_1 receptors are activated, the production of cAMP is inhibited, the permeability of voltage-gaited calcium channels is decreased, and potassium leak channels open [4]. The developing hyperpolarization prevents the release of glutamic acid and its involvement in the transmission of pain potentials [1, 5]. The use of cannabinoids as analgesics is limited due to their psychotropic properties, in particular the risk of catalepsy and drug addiction [2, 6].

Among 2*H*-chromene derivatives, the cannabinoid CB_1 receptor modulator, designated CHR, has the most pronounced analgesic activity [7, 8]. The CHR compound has a heterocyclic structure which is characteristic of cannabichromene. This cannabinoid has analgesic and anti-inflammatory effects [9].

The aim of this work was to study the analgesic activity, the effect on motor functions, and the potential ulcerogenic effect of a new 2*H*-chromene derivative, the cannabinoid CB_1 receptor modulator (codenamed CHR).

MATERIALS AND METHODS

The 2*H*-chromene derivative was (*2R,4aR,7R,8aR*)-4,7-dimethyl-2-(thiophene-2-yl)octahydro-2*H*-chromene-4-ol (Fig. 1). It was synthesized at Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences (Novosibirsk) [7].

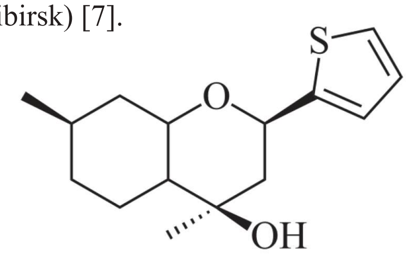

Fig. 1. Structural formula of the CHR compound

The experiments were carried out at the R&D Center (IPHAR LLC, Tomsk, Russia) on 96 specific pathogen-free male CD-1 mice and 15 male Sprague Dawley rats. The animals were kept in standard plastic cages (VELAZ, Czech Republic) at 20–23 °C and relative humidity of no more than 50%, with the exhaust – supply ratio of 8 : 10 and a 12 : 12 light / dark cycle. The animals were kept and cared for in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Directive 2010/63/EU). The study was conducted in compliance with the principles and rules of Good Laboratory Practice and approved by the Ethics Committees at Siberian State Medical University (Protocol 20/23 of 08.12.2023) and IPHAR LLC (Protocol 127/2022 of 14.02.2022).

In all experiments, the CHR compound at an effective dose of 5 mg / kg was orally administered to the animals 1 h before exposure to pain-inducing agents. The effective dose was determined in preliminary exploratory experiments. The CHR compound was dissolved in a 2% aqueous solution of Tween 80 (NeoFroxx GmbH, Germany). The control animals received this solvent according to the similar regime. Cannabinoid-based analgesics are not registered in the Russian Federation; therefore, the most frequently prescribed analgesics for pain control of different intensity were used as comparison drugs – the opioid analgesics tramadol at a dose of 20 mg / kg [10] and morphine at a dose of 4 mg / kg (both obtained from Moscow Endocrine Plant, Moscow, Russia) [11], and the non-steroidal anti-inflammatory drug diclofenac sodium at a dose of 10 mg / kg (Hemofarm, Serbia) [12, 13]. Aqueous solutions of tramadol and diclofenac sodium were orally administered to the animals, morphine was subcutaneously injected in isotonic sodium chloride solution. The mice were euthanized by cervical dislocation, the rats – by carbon dioxide.

Formalin test. Mice (4 groups, $n = 6$ animals per group) were injected with 0.02 ml of a 0.5% aqueous formalin solution (Sigma-Aldrich, USA) into the plantar aponeurosis of the hind limb. For 60 min, we recorded the pain response by the number of licks and shakes of the injured hind paw. In the first 10 min, the acute phase (phase 1) took place due to direct activation of nociceptors by algogens. In the next 50 min, the tonic phase (phase 2) caused by inflammation developed. After 60 min, the animals were euthanized, and the weight of their hind limb amputated at the ankle joint was measured [14].

Acetic acid-induced writhing test. Mice (4 groups, n = 6 animals per group) were intraperitoneally injected with 0.75% aqueous acetic acid solution (Sigma-Aldrich, USA) in a volume of 0.1 ml per 10 g of body weight. Within 20 minutes, we evaluated the number of abdominal muscle contractions (writhings) and the latency time to the first writhing [14].

Hot plate test. Mice (3 groups, n = 6 animals per group) were placed on a metal plate preheated to 55 ± 1 °C (HWT-75 thermal table, Russia). We measured the latency to the first pain response, which was registered by paw withdrawal and licking. The mice were kept on the hot plate for no more than 1 min to avoid injury [14].

Tail-flick test. The tails of mice (3 groups, n = 6 animals per group) were placed under the heat source of the laboratory analgesia meter (Hugo Sachs Elektronik, Germany). We measured the time until the tail was removed from the source [14].

The effect of the CHR compound on the motor function of mice was studied in the *open field test* (2 groups, n = 6 animals per group). The CHR compound was administered to mice at a dose of 5 mg / kg. Their motor activity was evaluated 1 h after the administration using the LE 8811 infrared actimeter and the ActiTrack software (Panlab, Spain) [14].

To study the potential ulcerogenic effect, intact rats (3 groups, n = 15 animals per group) were orally administered the CHR compound at a dose of 5 mg / kg or diclofenac sodium at a dose of 10 mg / kg four times (with an interval of 24 h). Three hours after the last administration, the animals were euthanized, and the condition of their gastric mucosa was assessed using the dissecting microscope (Observational Instruments, Saint Petersburg, Russia) at ×10. The degree of mucosal damage was graded in points: 0 – no damage, 0.5 – localized mucosal hyperemia, 1 – generalized mucosal hyperemia covering most (> 50%) or all of the gastric mucosa, 2 – the presence of up to three hemorrhages without erosion, 3 – the presence of more than three hemorrhages or erosions, 4 – the presence of more than three erosions or no more than two ulcers, 5 – the presence of more than two ulcers, total thinning of the gastric mucosa [14].

The results were statistically processed using the Statistica v. 8.0 software (StatSoft, USA). The Shapiro – Wilk test showed that the data were not normally distributed and were presented as the median and the interquartile range Me (Q_1; Q_3). The sample sizes were minimally sufficient for statistical analysis and complied with 3Rs [15]. The statistical significance of the differences between the groups was assessed using the Kruskal – Wallis test followed by the Mann – Whitney test for post-hoc pairwise comparisons. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In the formalin test, the CHR compound at a dose of 5 mg / kg reduced the number of licks and shakes of the damaged hind limb in the mice in the acute phase (response to algogen) by 43% and in the tonic phase – by 63% ($p < 0.05$, Table 1). The effects of the CHR compound were no weaker than those of morphine at a dose of 4 mg / kg and tramadol at a dose of 20 mg / kg ($p > 0.05$). Both opioid analgesics reduced the number of pain responses in both phases by 47–83%. The limb weight in the mice that received the CHR compound was 45 (36; 55) mg and did not differ from that in the mice that received Tween 80 (47 (38; 49) mg). This means that the analgesic effect of the 2*H*-chromene derivative CHR is not associated with an antiinflammatory effect.

Table 1

The number of pain responses in the formalin test at oral administration of the CHR compound (5 mg/kg), tramadol (20 mg/kg), and morphine (4 mg/kg) to the mice, Me (Q_1; Q_3), n = 6

Number of pain responses	2% aqueous solution of Tween 80 (control)	CHR compound	Tramadol	Morphine
Acute phase	54 (52; 56)	30 (26; 34)*	32 (24; 38)*	26 (24; 28)*
Tonic phase	24 (20; 25)	9 (5; 13)*	4 (3; 5)*	2 (1; 7)*

* here and in Table 2 $p < 0.05$ compared to the control values.

In the acute visceral pain model, the CHR compound exhibited an analgesic effect that was comparable to that of diclofenac sodium and tramadol ($p < 0.05$, Table 2). The CHR compound reduced the number of writhings by 50%, diclofenac sodium and tramadol — by 52 and 56%, respectively. At the same time, the CHR compound did not affect the latency time to the first writhing and did not increase the pain threshold.

Table 2

Analgesic activity of the CHR compound (5 mg / kg), diclofenac sodium (10 mg / kg), and tramadol (20 mg / kg) when administered orally to the mice in the acetic acid-induced writhing test, *Me* (Q_1; Q_3), *n* = 6

Parameter	2% aqueous solution of Tween 80 (control)	CHR compound	Diclofenac sodium	Tramadol
Latency to the first writhing, sec	330 (315; 332)	507 (505; 508)	665 (660; 669)*	326 (316; 331)
Number of writhings	22 (21; 23)	12 (10; 13)*	11 (8; 15)*	11 (8; 14)*

In the hot plate test, the CHR compound at a dose of 5 mg / kg increased the latency time to the pain response by 34% ($p < 0.05$), whereas tramadol at a dose of 20 mg / kg increased this parameter by 49% ($p < 0.05$). The analgesic effect of the CHR compound at a dose of 5 mg / kg was comparable to that of tramadol ($p > 0.05$, Fig. 2).

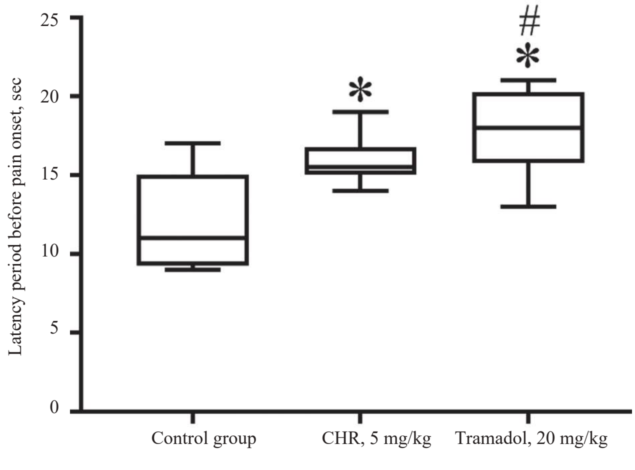

Fig. 2. Response latency in the hot plate test after oral administration of the CHR compound and tramadol to the mice. * differences with the control group (administration of Tween 80), $p < 0.05$, # differences with the CHR group, $p > 0.05$

The CHR compound at a dose of 5 mg / kg increased the tail-flick latency by 1.3 times, and tramadol at a dose of 20 mg / kg doubled this parameter. These values differed from the control group (administration of Tween 80) ($p < 0.05$). The analgesic effect of the CHR compound in this model was weaker than that of tramadol ($p < 0.05$).

The motor activity parameters of the mice that were administered the CHR compound at a dose of 5 mg / kg were comparable to those of the animals in the control group (administration of Tween 80) ($p > 0.05$, Table 3). The CHR compound at an effective dose did not affect the behavior of the animals in the open field test.

Table 3

Effect of the CHR compound (5 mg / kg) on the motor activity of the mice in the open field test, *Me* (Q_1; Q_3), *n* = 6

Parameter	2% aqueous solution of Tween 80 (control)	CHR compound
Number of movements	146 (119; 147)	131 (110; 153)
Average speed of movements, cm / sec	1 (0; 1)	1 (1; 2)
Total distance traveled, cm	54 (34; 59)	66 (35; 77)
Number of rears	2 (0; 4)	5 (5; 6)

NSAIDs and analgesics, especially non-selective cyclooxygenase inhibitors, have an ulcerogenic effect. It was interesting to study the effect of a new 2*H*-chromene derivative with non-steroidal analgesic properties on the gastric mucosa. Multiple administration of the CHR compound did not cause hyperemia, erosion or gastric ulcers. The degree of damage was 1 (1; 1) point and did not differ from that in the control group ($p > 0.05$). After multiple administration of diclofenac sodium at a dose of 10 mg / kg, the gastric mucosa became thinner; total hyperemia, multiple erosions and ulcers were detected. The degree of damage was 5 (5; 5) points ($p < 0.05$). Multiple oral administration of the CHR compound at an effective dose had no ulcerogenic effect and probably did not inhibit cyclooxygenase-1 [16].

The CHR derivative exhibited high analgesic activity in models of chemogenic pain induced by formalin and acetic acid. In the formalin test, the analgesic equally reduced the number of pain responses in the acute and tonic phases without affecting inflammation. It can be assumed that the CHR compound activated CB_1 receptors and caused hyperpolarization of afferent pain pathways in spinal and supraspinal structures [9].

In the thermal nociception models, the CHR compound showed a greater analgesic effect in the hot plate test, when the pain response involved predominantly supraspinal structures, such as nucleus raphe magnus, periaqueductal gray matter, limbic system, and cerebral cortex [14]. In the tail-flick test, the pain response was associated with the activation of predominantly the spinal ganglia and dorsal horns of the spinal cord. Therefore, the effect of the CHR compound was weaker [14]. Activation of CB_1 receptors in supraspinal structures makes the greatest contribution to the mechanisms of analgesic effects of the CHR compound.

According to *in vitro* studies, the CHR compound does not directly bind to cannabinoid receptors and does not affect the activity of enzymes involved in the endogenous cannabinoid metabolic pathway. However, its analgesic effects are inhibited by the CB_1 receptor antagonist rimonabant [17]. This indicates the ability of the CHR compound to activate CB_1 receptors indirectly. One of the probable mechanisms is binding to an allosteric site of the CB_1 receptor, which changes their conformation and increases their affinity for endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol [18, 19]. Unlike diclofenac sodium, the CHR compound does not have the ulcerogenic effect that is characteristic of NSAIDs. It also does not affect the motor activity of the animals.

CONCLUSION

The study demonstrated the analgesic activity of the 2*H*-chromene derivative CHR in mouse models of chemogenic, visceral, and thermal pain. The analgesic effect of the CHR compound in chemogenic pain models and in the hot plate test is the same as the effects of tramadol, morphine, and diclofenac sodium. The proposed mechanism of action of the CHR compound consists in modulation of the allosteric site of CB_1 receptors, which leads to an increase in their affinity for endocannabinoids. The studied analgesic does not damage the gastric mucosa and does not inhibit the motor activity of animals. The 2*H*-chromene derivative CHR is a promising drug for the pharmacotherapy of pain.

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Authors' contribution

Bykov V.V., Larchenko V.V. – conception and design. Gurkin N.V., Bykova A.V., Motov V.S. – carrying out of the experiments, analysis and interpretation of the data. Il'ina I.V., Volcho K.P., Salakhutdinov N.F. – chemical synthesis of the CHR compound. Khazanov V.A. – justification of the manuscript, critical revision of the manuscript for important intellectual content. Vengerovskii A.I. – final editing of the article and final approval of the article for publication.

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