folia medica

Folia Medica 61(4): 540-4
DOI: 10.3897/folmed.61.e47957

Original Article

Subchronic Central Administration of Cannabinoid Ligands Modulates Nociception in Bulbectomized Rats

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Received: 07 Nov 2018 ♦ **Accepted:** 06 June 2019 ♦ **Published:** 31 Dec 2019

Citation: Tashev R, Stavreva GT, Velikova MS. Subchronic central administration of cannabinoid ligands modulates nociception in bulbectomized rats. Folia Med (Plovdiv) 2019;61(4):540-4. doi: 10.3897/folmed.61.e47957.

Abstract

Introduction: Endocannabinoid system is involved in neuropsychiatric disorders such as major depression. The bilaterally olfactory bulbectomized rat is widely used as an animal model of depression. The removal of the olfactory bulbs produces behavioural, physiological, and neurochemical alterations resembling clinical depression. There is increasing evidence that highlights the important role of cannabinoid signalling in depression and nociception.

Aim: To investigate the effect of CB1 receptor agonist HU 210 and CB1 receptor antagonist SR 141716A administered icv subchronically (for 7 days) on nociception of rats with model of depression - bilateral olfactory bulbectomy (OBX).

Material and methods: Experimental model of depression - bilateral olfactory bulbectomy (OBX). Bilaterally olfactory bulbectomized rats were used as an experimental model of depression. HU 210 (5 μg) or SR 141716A (3 μg) were infused icv for 7 consecutive days, starting 15 days after the olfactory bulbectomy. Nociception was examined by applying paw pressure test (analgesy-meter) evaluating the rat pain threshold. On day 7, five minutes after the last microinjection, the rats were tested in an analgesy-meter and their mechanically evoked pain responses were measured in arbitrary units (AU).

Results: Microinjections of HU 210 (5 μg) significantly decreased the pain threshold in olfactory bulbectomized rats, while SR 141716A (3 μg) exerted antinociceptive effect by increasing the pain threshold.

Conclusions: Data point to an involvement of CB1 receptors in depression-like behaviour and nociception in olfactory bulbectomized rats and support the data for the association between depressive disorder and pain pathways.

Key words

CB1 cannabinoid receptors, depression, nociception, olfactory bulbectomy, rat

INTRODUCTION

Clinical data are present about close association of depressive disorders and pain. Interactions between pain perception and depressive symptoms in patients have been described.[1] Most of the patients with depression and pain do not respond to the pharmacological treatments.[2]

The bilateral olfactory bulbectomy (OBX) syndrome in rats has been proposed as an animal model of depression.[3] OBX is associated with changes in behaviour, and in the

endocrine, immune, and neurotransmitter systems, which simulate many of these seen in patients with major depression.[4]

Recently, the endocannabinoid system has attracted much attention in relation to involvement in neuropsychiatric disorders such as major depression.

The endocannabinoid system is a biological system composed of endocannabinoids, cannabinoid receptors and the enzymes involved in the synthesis and inactivation of the neurotransmitters.[5,6] Endocannabinoid signalling system has an important regulatory role throughout the nervous system that makes it potential therapeutic target for a wide range of disorders, including chronic pain, nausea, inflammation, cancer, cardiovascular disease, spasticity, epilepsy and immunomodulation.[7]

The biological effects of cannabinoids are mediated via binding to type 1 (CB1) and type 2 (CB2) cannabinoid receptors which belong to the family of G-protein-coupled receptors.[5] The effects of cannabinoids in the central nervous system are mediated mainly by CB1 receptors. They are expressed at high density in different brain areas, where can be found mainly on the presynaptic nerve terminals.[8] Cannabinoid CB1 receptors are present also in brain regions involved in nociceptive perception, such as the thalamus, amygdala and brainstem.[9,10] Numerous literature data provide evidence that cannabinoids produce antinociception by acting at peripheral, spinal, and supraspinal sites.[11]

In the last few years, it has been found that the brain endocannabinoid system is involved in neuropsychiatric disorders such as major depression. There is increasing evidence that highlights the important role of the cannabinoid signalling in depression and nociception.[12,13]

The synthetic cannabinoid derivative HU 210 shows high potency to the CB1 receptors, whereas SR 141716A acts as a CB1 receptor antagonist.

AIM

The aim of the present study was to investigate the effect of CB1 receptor agonist HU 210 and CB1 receptor antagonist SR 141716A administered icv subchronically (for 7 days) on nociception of rats with experimental model of depression - bilateral olfactory bulbectomy.

MATERIALS AND METHODS

The experiments were carried out on 42 male Wistar rats (200-240 g at the time of surgery). The experiments were performed according to the Guide to the Care and Use of Experimental Animals of the Ethics Committee of the Institute of Neurobiology, Bulgarian Academy of Sciences.

Experimental model of depression - bilateral olfactory bulbectomy (OBX)

Bilateral olfactory bulbectomy was performed according to the method previously described.[3] The animals were anesthetized and placed in a stereotaxic apparatus (Stoelting, USA) and guide cannulae were implanted into ventriculus ventrolateralis dextra. One µl of drug solution HU 210 (5 µg) or SR 141716A (3 µg) were infused icv for 7 consecutive days, starting 15 days after the OBX procedure. On day 7, five minutes after the last microinjection, the rats were tested in an analgesy-meter.

Analgesy-meter test (paw-pressure)

The changes in the nociceptive response were determined by the foot-pressure method. A constantly increasing pressure was applied to the dorsal surface of the hind paw. The actual load applied was recorded in arbitrary units (AU) when the animal made its first escape attempt.

The animals were divided in two main clusters: cluster I consisting of group 1 - sham operated rats injected icv with saline; group 2 - sham operated rats + HU 210; group 3 - sham operated rat + SR141716A; cluster II consisting of group 1 - OBX+saline; group 2 - OBX+HU 210; and group 3 - OBX + SR141716.

Statistical analysis

Data were analysed by one-way ANOVA and further analysed by post hoc Student-Newman-Keuls (SNK) test.

RESULTS

Effects of HU 210 and SR 141716A infused icv in rats on nociception.

ANOVA demonstrated a significant effect for factor drug ($F_{2,20}$ = 23,7311; $p \leq 0.001$) on pain threshold. HU 210 significantly increased ($p \leq 0.001$) while the CB1 antagonist SR 141716A decreased the pain threshold ($p \leq 0.05$) as compared to the saline treated sham operated controls (**Fig. 1**).

Effects of HU 210 and SR 141716A infused icv in OBX rats on nociception.

ANOVA showed a significance for factor bulbectomy ($F_{1,14}$ = 48,731; $p \leq 0.001$). Post-hoc SNK test demonstrated that the olfactory bulbectomy increased the pain threshold ($p \leq 0.001$) as compared to the sham operated controls. ANOVA demonstrated a significant effect for factor drug ($F_{2,20}$ = 18,8280; $p \leq 0.001$).

HU-210, administered icv for 7 days in OBX rats decreased the pain threshold ($p \leq 0.001$), while SR 141716A increased it ($p \leq 0.05$) as compared to the saline treated OBX rats (**Fig. 2**).

The comparison of the effects of the CB1 ligands in OBX rats to the effects exerted in the sham operated rats, revealed that HU 210 increased pain threshold ($p \leq 0.002$), while SR 141716A produced a significant antinociceptive effect by increasing the pain threshold in comparison to both sham-operated rats ($p \leq 0.001$) and HU 210 treated OBX rats ($p \leq 0.001$) (**Fig. 2**).

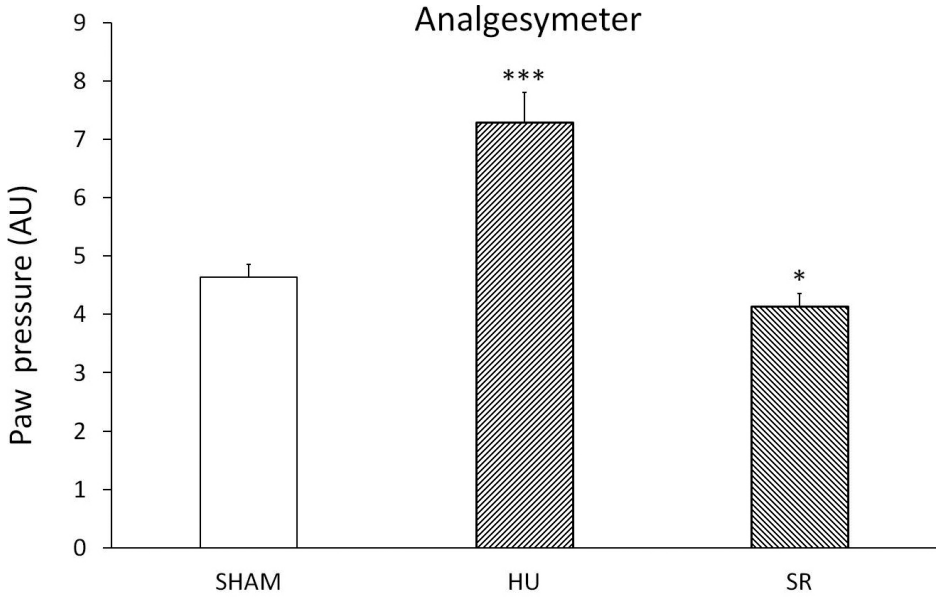

Figure 1. Effects of HU-210 (5 μg) and SR 141716A (3 μg), microinjected icv for 7 days on pain threshold (AU). n = 7. *$p \leq 0.05$; ***$p \leq 0.001$ – comparisons vs. saline-treated controls. Means (± S.E.M.) are presented.

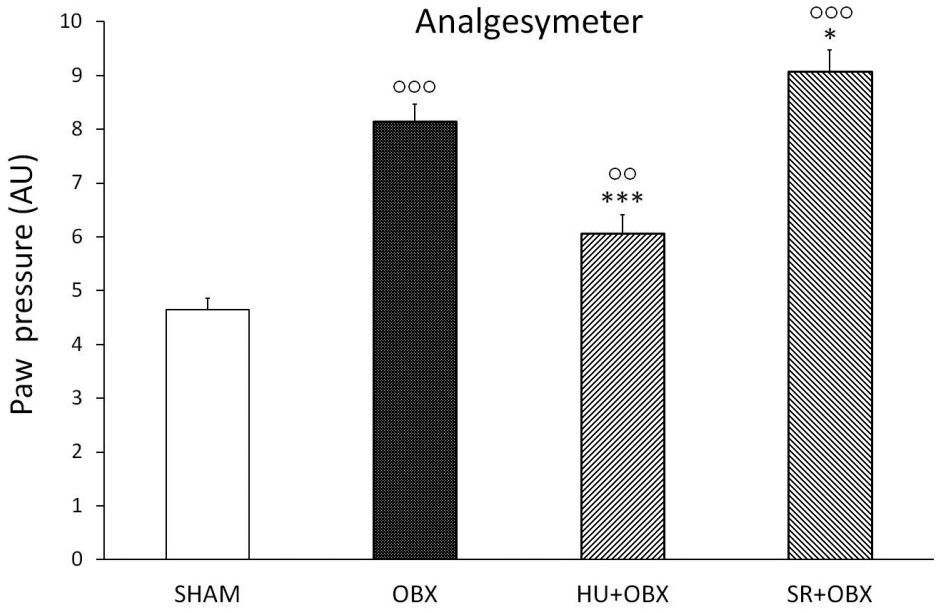

Figure 2. Effects of HU-210 (5 μg) and SR141716A (3 μg), microinjected icv for 7 days on nociception in OBX rats. Asterisks indicate comparisons of pain threshold (AU) in HU-210-treated OBX rats or SR141716A-treated OBX rats vs. OBX saline-treated rats. *$p \leq 0.05$; ***$p \leq 0.001$. Circles depict comparisons after OBX rats microinjected with HU-210 or SR141716A vs. sham operated saline-treated rats. n = 7. ^{oo} $p \leq 0.002$; ^{ooo} $p \leq 0.001$. Means (± S.E.M.) are presented.

DISCUSSION

The present study extended the understanding about the effects of cannabinoid ligands applied subchronically (7 days) icv on nociception of OBX rats. The CB1 receptors agonist HU-210 decreased pain sensitivity, i.e. exerted antinociceptive effect in the paw pressure test, while the CB1 receptor antagonist SR 141716A increased pain sensitivity to mechanical pressure i.e., produced hyperalgesia. Many animal models of depression support the clinical relationship between depression and pain.[14,15] The clinical data have been confirmed in various experimental models of depression and pain.[15] Olfactory bulbectomy in rats is a widely used experimental model of depression which resembles major

depression.[4] Removal of the olfactory bulbs leads to many behavioural, biochemical and cellular changes that are similar to the ones found in depressed patients. The lesion of the olfactory bulbs results in neurodegeneration in the different brain regions (cortex, amygdala and hippocampus) as the bulbs send projections to these areas. OBX syndrome is believed to result from dysfunction in brainstem and limbic areas accompanied by changes in many neurotransmitter systems.[3]

Previously we have described an increased pain threshold of OBX rats, as compared to the sham operated controls, using Randall-Selitto analgesy-meter. Now we have found nociceptive effect of HU-210 by decreasing the pain threshold of OBX rats, while SR 141716A increased the pain threshold in OBX rats only compared to the sham-operated controls. As far as olfactory bulbectomy reduces the nociceptive response of rats in the analgesy-meter test, the effect of HU- 210 could be interpreted as a tendency for an improvement of the nociceptive response.[16,17]

Previously we have found similar effects upon acute icv injection of HU-210 and SR 141716A.[17] Recently, it has been shown that cannabinoids play a role in nociceptive processes although the exact mechanisms by which they interfere in these processes are not well established.[18-21]

CONCLUSIONS

The results suggest an involvement of CB1 receptors in depression-like behaviour and nociception in OBX rats and support the evidence of the association between depressive disorder and pain pathways. The CB1 receptor ligands and especially the CB1 receptors agonists may be applied as potential antidepressant and analgesic agents although additional studies have to reveal their involvement in the mechanisms of depression and pain.

ACKNOWLEDGEMENTS

This study was supported by MU-Varna, Grant № AD-008-1/06.04.2012.

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Субхроническое центральное применение ноцицепции модуля каннабиноидного лиганда у бульбэктомизированных крыс

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Дата получения: : 07 ноября 2018 ♦ **Дата приемки:** 06 июня 2019 ♦ **Дата публикации:** 31 декабря 2019

Образец цитирования: Tashev R, Stavreva GT, Velikova MS. Subchronic central administration of cannabinoid ligands modulates nociception in bulbectomized rats. Folia Med (Plovdiv) 2019;61(4):540-4. doi: 10.3897/folmed.61.e47957.

Абстракт

Введение: Эндоканнабиноидная система связана с психоневрологическими расстройствами, такими как тяжёлая депрессия. Двусторонняя ольфакторно бульбэктомизированная крыса широко используется в качестве животной модели депрессии. Удаление обонятельных луковиц вызывает поведенческие, физиологические и нейрохимические изменения, сходные с таковыми при клинической депрессии. Появляется все больше доказательств в поддержку важной роли передачи сигналов каннабиноидов при депрессии и ноцицепции.

Цель: Изучить влияние агониста рецептора CB1 HU 210 и антагониста рецептора CB1 SR 141716A, вводимого интрацеребровентрикулярно (подкожно) (в течение 7 дней), на ноцицепцию крыс с помощью модели депрессии-двусторонней ольфакторной бульбэктомии (ОБЭ).

Материалы и методы: Экспериментальная модель депрессии - двусторонняя ольфакторная бульбэктомия (ОБЭ). В качестве экспериментальной модели депрессии использовали двухсторонне ольфакторно бульбэктомизированных крыс. HU 210 (5 μg) или SR 141716A (3 μg) вводили в течение 7 дней подряд, начиная с 15 дня после ольфаторной бульбэктомии. Ноцицепция была исследована с использованием paw pressure test (PPT) (анальгезиметр) для определения порога боли у крыс. На седьмой день, через пять минут после последней микроинъекции, крыс тестировали анальгезиметром, и их ответы на механически вызванную боль измеряли в произвольных единицах (arbitrary units (AU)).

Результаты: Микроинъекции HU 210 (5 μg) значительно снижали болевой порог у ольфакторно бульбэктомизированных крыс, тогда как SR 141716A (3 μg) оказывал антиноцицептивный эффект, увеличивая болевой порог.

Выводы: Данные указывают на участие рецепторов CB1 в депрессоподобном поведении и ноцицепции у ольфакторно бульбэктомизированных крыс и подтверждают данные о связи между депрессивными расстройствами и болевыми путями.

Ключевые слова

CB1 каннабиноидные рецепторы, депрессия, ноцицепция, ольфакторная бульбэктомия, крыса