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TOLERANCE TO CANNABINOIDS IN MICE

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Abstract:

The *Cannabis sativa* plant, for its analgesic, anti-inflammatory, antiemetic, and anticonvulsant properties, has been used for thousands of years in Chinese, Indian, and Greek cultures and was introduced into Western medicine in the 19th century. There has been a rise in interest in cannabinoids since the main substances of cannabis were identified, as well as the recognition that the endocannabinoid system (ECS) controls multiple processes in pain treatment and neurologic and mental illnesses. However, the ECS has also been associated with negative effects, including harmful effects on emotional and cognitive functions, the development of tolerance and dependence, and withdrawal symptoms after drug cessation in humans. We recently found that repeated intraperitoneal administration of the two main components of cannabis, delta-9-tetrahydrocannabinol (THC) and cannabinolic acid (CBNA), led to the development of tolerance in male mice. In this review, we focus on the evidence demonstrating cannabinoid tolerance in animals. The common mechanisms and main signaling pathways for cannabinoid tolerance, including neuroadaptations primarily at cannabinoid 1 (CB1) receptors, such as desensitization and downregulation, which are mediated by several signaling pathways, are discussed.

Keywords: analgesia, cannabis use disorder, desensitization, nociception, pain.

INTRODUCTION

Cannabis extracts were used to treat psychiatric problems at the turn of the 20th century and were particularly effective as sedatives and hypnotics [24, 37]. Cannabis usage for medical purposes, including in psychiatry, significantly decreased after the 1930s, since it was considered an illegal narcotic. The discovery that the endocannabinoid system (ECS) can alter multiple processes in pain management and psychiatric disorders, as well as the identification of the main ingredients in cannabis, has reignited interest in the use of cannabinoids [11, 15, 17, 23, 32]. Eight European countries legalized the use of cannabis extracts for medical reasons in 2010 [7]. Three

species of the cannabis plant, including *C. sativa, C. indica, and C. ruderalis*, make up the genus. These plants contain more than 560 known chemicals, of which 150 are phytocannabinoids, even though the contents differ between particular strains and species [30].

ENDOCANNABINOID SYSTEM

Even though cannabis has long been used as a traditional remedy for a wide range of illnesses, regulated clinical research on the plant's effectiveness has just now started to emerge. Numerous noteworthy advancements in the fields of cannabis science and the finding of ECS in the mammalian brain have occurred throughout the last fifty years. In addition, there has been a notable rise in interest in the potential analgesic effects of cannabis over the last ten years [1, 5, 6, 28].

Many techniques that interfere with the ECS have been created in the last 20 years, and they have shown promise in treating neurological diseases and pain. Global targeting of the ECS, however, is also linked to unfavorable outcomes, such as detrimental effects on mood, memory, and cognition, as well as the development of human dependence and tolerance [5, 18, 32, 33, 42]. Similarly, laboratory animals also exhibit both dependence and tolerance following the chronic use of cannabinoids [2, 18, 25, 36].

The ECS is involved in pain, perception, learning and memory, movement, digestive regulation, and control of mechanisms of sleep, the pulmonary, autonomic, and immunomodulatory systems. Components of the cannabinoid system are expressed almost ubiquitously throughout nociceptive pathways, thus targeting the system via exogenous cannabinoid ligands or enhancement of endogenous communication regulating nociceptive signaling at multiple sites: in the periphery, the dorsal horn of the spinal cord, and pain-associated regions of the brain [42].

The ECS is implicated in pain signaling pathways. It consists of the cannabinoid 1 receptor (CB1) and cannabinoid 2 receptor (CB2), endogenous ligands (or endocannabinoids), and metabolizing their enzymes. Cannabinoids are a diverse class of biologically active constituents of cannabis or synthetic compounds, which usually have an affinity for and activity at cannabinoid receptors [35]. Based on their origin, they are classified into three categories: phytocannabinoids (plant-derived), endocannabinoids (present endogenously in human tissues), and synthetic cannabinoids (pharmaceutical). Cannabinoids exert an analgesic effect, particularly in hyperalgesic conditions associated with neuropathic and inflammatory pain [29]. Components of the cannabinoid system are found in almost all nociceptive pathways, including the periphery, dorsal horn of the spinal cord, and brain structures associated with pain processing [42], including parts of the limbic system (amygdala, cingulate, and insular cortices) [39–41]. Thus, nociceptive signaling occurs by modulating effects at multiple sites through exogenous cannabinoid ligands or enhancing endogenous communication [42].

ENDOCANNABINOID RECEPTORS

The first cannabinoids obtained from the dried flowers of *C. sativa cultivars* used to produce marijuana and hemp, respectively, were chemically characterized as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). CBD has a non-psychotropic effect, while THC has a psychoactive effect. THC works via two G protein-coupled receptors (GPCRs), CB1 and CB2 receptors, of which CB1 answers for the psychoactive impacts of cannabis. However, no particular receptor for CBD has been identified to date. However, several molecular targets have been suggested to mediate the unmistakable impacts of this cannabinoid [6]. It is interesting that, although CBD has long been utilized in cannabis-based preparations, compared to other cannabis constituents, it has historically attracted much less attention as a single medicine. Due to its advantageous neuroprotective, antiepileptic, anxiolytic, antipsychotic, and anti-inflammatory qualities, CBD is currently generating a lot of interest. As

a result, medicinal chemists are becoming more and more interested in the CBD scaffold [27].

Following the identification of CB1, mainly expressed in the brain, and CB2, expressed predominantly in immune cells and during inflammatory injury in the CNS, endogenous ligands for these proteins were isolated and characterized. The first is N-arachidonoyl-ethanolamine (AEA), named 'anandamide' for the Sanskrit word for 'bliss.' The second is 2 arachidonoyl-glycerol (2 AG), which were named the endocannabinoids. This system of two signaling lipids, their two receptors, and five main enzymes for their biosynthesis and inactivation became known as the endocannabinoid system (ECS). This system was soon assigned a wide variety of physiological actions that extended well beyond what could be predicted from the pharmacological effects of THC. Later, it was discovered that changes in endocannabinoid signaling were related to a variety of pathological conditions. These changes were caused by modifications in the expression and function of cannabinoid receptors and endocannabinoid metabolic enzymes [4, 6, 19, 23].

Since the discovery of cannabinoid receptors and their endogenous ligands, the ECS has been regularly regarded as a putative target for the treatment of neuropathic and inflammatory pain, cancer, obesity, and several pathologies, including neurodegenerative diseases. Nevertheless, the potential clinical uses of cannabinoids remain strongly limited by the unacceptable adverse effects of cannabis, including its psychotropic action [1, 17] or tolerance, dependence, and withdrawal symptoms upon drug cessation [18, 30].

Moreover, a wide range of synthetic cannabinoids, besides cannabis and oral and inhaled formulations of THC, are commonly used for recreational purposes. These synthetic cannabinoids are highly potent full agonists at CB1 and CB2 receptors and bind with a 10-100 times higher binding affinity compared to THC. These synthetic cannabinoids also exhibit increased potency relative to THC in preclinical animal models [9].

Agonist activation of the CB1 receptor has been shown to lead to stimulation of mitogen-activated protein kinases (MAPK) and G protein-coupled inward rectifying potassium channels (GIRKs) as well as inhibition of adenylyl cyclase (AC) and voltage-gated calcium channels (VGCCs). Functional selectivity has been demonstrated for CB1 receptors with specific agonists exerting distinct and differential modulatory effects on these signaling pathways [30].

CANNABINOID TOLERANCE

A wide range of studies have revealed tolerance to the effects of THC, or inhaled cannabis, in human subjects [10, 13, 16, 22]. Tolerance to the psychomimetic, amnestic, perceptual, anxiogenic, and cortisol-increasing effects of intravenous THC has been demonstrated in frequent cannabis users [8, 31]. Interestingly, the euphoric effects of intravenous THC were not blunted in cannabis users, providing evidence that tolerance and the neuroadaptations associated with this process might develop in response- and brain region-specific manner [8]. Other studies have shown that tolerance develops to the intoxicating "high" effects of oral THC [10] as well as the acute effects of THC on functional connectivity between regions of the brain involved in reward signaling such as the ventral palladium, nucleus accumbens, and cerebral cortex [22, 30].

As the ability to probe pharmacodynamic changes in CB1 receptors in humans using positron emission tomography (PET) radioligands was developed, it became evident that pharmacodynamic neuroadaptations in CB1 receptors played a critical role in cannabinoid tolerance. These studies have demonstrated that the CB1 receptor is downregulated in cannabis users meeting the diagnostic criteria for cannabis use disorder (CUD). Downregulation of CB1 receptors in cannabis users was less profound in subcortical brain regions compared to cortical regions. This pattern was found in humans as well as in animal models [30].

In particular, cannabinoid agonists have been shown to elicit well-characterized "tetrad"

(antinociception, hypothermia, catalepsy, and hypoactivity) effects in rodents that include tail-flick antinociception, decreased body temperature, decreased locomotor activity, and catalepsy. Moreover, tetrad effects are absent in CB1 knockout (KO) mice or mice treated with CB1 antagonists such as rimonabant [14, 26, 30].

We have recently shown that systemic (intraperitoneal, i.p.) administration of 25 μg/kg THC induced strong antinociception in all three behavioral tests on the first day of the experiment. From the second day of testing, the latency of the withdrawal reflex is progressively reduced, indicating the development of tolerance to repeated systemic administration of THC [38]. In the second series of experiments, we explored a 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, faster tolerance than THC.

Repeated i.p. administration of CBNA resulted in a gradual decrease in antinociception in the behavioral measures. Withdrawal responses to heat and mechanical stimuli returned to baseline by the 4^{th} or 5^{th} day of testing, respectively. Therefore, as for THC, tolerance developed following repeated administration of CBNA. Our results, thus, showed that while the two main components of cannabis, THC and CBNA, produced strong antinociceptive effects on thermal and mechanical stimuli in mice, their repeated systemic administration resulted in rapid tolerance, showing that within 4-5 days after the introduction, the withdrawal reactions returned to their original control values [38].

Other research has demonstrated tolerance develops at different rates for many cannabinoid agonists with synthetic, high-potency, full-cannabinoids, such as 0.3 mg/kg CP55,940, often showing slower tolerance compared to 30 mg/kg THC in mice.

According to recent research, habitual cannabis users tend to experience the effects of acute THC delivery less noticeably than non-users. These studies suggest that after acute THC delivery, regular cannabis users experience impairments in a wide variety of cognitive abilities. Accordingly, human cognitive abilities (such as sustained attention, psychomotor prowess, distractibility, verbal learning, etc.) seem to be the domain most likely to exhibit tolerance after repeated exposure, with some evidence of full tolerance indicating a complete lack of an acute effect [3]. Activation of cannabinoid receptors, accumulation of cannabinoids and their metabolites, and elevation of neuroinflammatory cytokines are just a few of the pathways that cannabinoids and their metabolites can go through to have negative consequences when THC is administered repeatedly. As a result, the chain of neurobiological events that result in illnesses impacting brain chemistry and circuitry may include tolerance [3]. Therefore, we recommend considering this possibility when prescribing cannabis-based pain drugs.

It can be concluded that exposure to cannabinoids leads to suppression of nociceptive processing and reduction of pain. Peripheral, spinal, and supraspinal mechanisms are involved in the implementation of this suppression. Cannabinoids reduce the sensitization and hyperexcitability of neurons, as well as hyperalgesia and allodynia. Their effect is realized by modulating nociceptive transmission through the CB1 and CB2 receptors, located in the peripheral areas and spinal cord [2, 12, 20, 29, 34]. Thus, cannabinoids may be used as an alternative to opioids or as an adjunct medication to reduce the doses of opioids required for analgesia.

Traditionally, tolerance to cannabinoid compounds has been associated with downregulation and desensitization of CB1 receptors, and the role of CB2 receptors in tolerance, conversely, is thought to be minimal [21]. However, recent investigation into the mechanisms of cannabinoid tolerance has revealed possible mechanisms for CB2 receptor downregulation. So, this critical question remains largely unanswered, and this knowledge gap requires additional investigation [30].

Many studies have shown that for cannabinoid tolerance, phosphorylation of CB1

receptors by GIRKs and subsequent recruitment of β-arrestin2 play a critical role in CB1 neuroadaptations. Most animal studies of cannabinoid tolerance are limited to the effects of isolated purified cannabinoid compounds such as THC, CBD, synthetic CP55,940, and WIN55,212-2. However, the study of tolerance to cannabis in general, which contains many cannabinoid and terpene components, is not yet well understood. There is some evidence showing the modulating effects of various components of cannabinoid mixtures. Thus, different sensitive areas may participate in tolerance mechanisms depending on the specific mixture of compounds affecting them [30].

CONCLUSION

This review summarizes current knowledge of the mechanisms and signaling pathways that are responsible for cannabinoid tolerance obtained in human and animal models. These neuroadaptive mechanisms include down-regulation and desensitization of CB1 receptors, which are mediated by several signaling pathways and components, including β-arrestin2, GIRK, c-Jun N-terminal kinases (JNK), PKA, and nitric oxide (NO). However, CB1 suppression during neuroadaptation has been demonstrated in human cannabis users, while the desensitization process has only been demonstrated in animal models where appropriate tools exist to evaluate this process. The development of a neuroimaging tool to visualize CB1 receptor desensitization in humans will allow further assessment of the possible contribution of this process to cannabinoid tolerance in humans. The use of this new technique will also reveal the desensitization pattern of other GPCRs, including opioid receptors [30].

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ТОЛЕРАНТНОСТЬ К КАННАБИНОИДАМ У МЫШЕЙ

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Растение *Cannabis sativa*, на протяжении тысячелетий использовалось в китайской, индийской и греческой культурах и было введено в западную медицину в 19 веке из-за ее болеутоляющего, противовоспалительного, противорвотного и противосудорожного свойств. После идентификации основных компонентов каннабиса и открытия эндоканнабиноидной системы (ЭКС), модулирующей различные процессы в лечении боли и психических расстройствах, интерес к каннабиноидам возобновился. Исследования продемонстрировали потенциальную эффективность ЭКС в облегчении боли и неврологических расстройств. Однако ЭКС также связана с негативными проявлениями, включая вредное воздействие на эмоциональные и когнитивные функции, развитие толерантности и

зависимости, а также симптомы абстиненции после прекращения приема наркотиков у людей. Недавно мы обнаружили, что повторяющееся внутрибрюшинное введение двух основных компонентов каннабиса, дельта-9-тетрагидроканнабинола (ТГК) и каннабиноловой кислоты (КНБК), приводит к развитию толерантности у мышей-самцов. В этом обзоре мы обобщили сведения, демонстрирующие толерантность к каннабиноидам у животных, обсуждая общие механизмы и основные сигнальные пути толерантности к каннабиноидам, включая нейроадаптацию, прежде всего на рецепторах каннабиноида 1 (CB1), такие как десенсибилизация и подавление регуляции, которые опосредуются несколькими сигнальными путями.

Ключевые слова: анальгезия; расстройство, связанное с употреблением каннабиса; десенситизация; ноцицепция; боль

SİÇANLARDA KANABİNOİDLƏRƏ DÖZÜMLÜLÜK

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Cannabis sativa bitkisi min illərdir Çin, Hindistan və Yunan mədəniyyətlərində istifadə olunmuşdur və 19-cu əsrdə Qərb təbabətinə ağrıkəsici, iltihab əleyhinə, qusmaya qarşı və antikonvulsant xüsusiyyətlərinə görə tətbiq edilmişdir. Kanabisin əsas komponentlərinin müəyyən edilməsindən, ağrı və psixi pozulmaların müalicəsində müxtəlif prosesləri modulyasiya edən endokannabinoid sisteminin (EKS) kəşfindən sonra kannabinoidlərə maraq yenidən artmışdır. Tədqiqatlar EKS-nin ağrı və nevroloji pozulmaların aradan qaldırılmasında potensial effektivliyini nümayiş etdirdi. Bununla belə, EKS həm də mənfi təsirlərlə, o cümlədən emosional və koqnitiv fəaliyyətə zərərli təsirlər, dözümlülük və asılılığın inkişafı və insanlarda dərman dayandırıldıqdan sonra çəkilmə simptomları ilə əlaqələndirilir. Bu yaxınlarda aşkar etdik ki, kanabisin iki əsas komponenti olan delta-9-tetrahidrokannabinol (THK) və kannabinol turşusunun (KBNT) təkrar peritondaxili tətbiqi erkək siçanlarda tolerantlığın inkişafı ilə nəticələnir. Bu icmalda heyvanlarda kannabinoid tolerantlığını nümayiş etdirən dəlilləri ümumiləşdirərək, kannabinoid tolerantlığının ümumi mexanizmləri və əsas siqnal yolları, ilk növbədə kannabinoid 1 (CB1) reseptorlarında neyroadaptasiya, o cümlədən çoxlu siqnal yollarının vasitəçiliyi ilə həyata keçən desensitizasiya və aşağı düşən tənzimləmə müzakirə olunmuşdur.

Açar sözlər: analgeziya, kanabis ilə əlaqəli pozulma, desensitizasiya, nosisepsiya, ağrı

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