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Transient Retinal Dysfunctions after Acute Cannabis Use

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Key Words
Cannabis · Electroretinography · Retina · Synaptic transmission · Endocannabinoids · Lupus erythematosus

Abstract
Although cannabis is very widespread worldwide, the impact of cannabis on visual function remains poorly understood. This is partly due to numerous difficulties met in developing clinical studies in cannabis users. Here, we report the first documented case of neuroretinal dysfunction after acute cannabis smoking. This observation was favored by the need of an annual ophthalmic evaluation in the context of a chloroquine intake for a systemic lupus erythematosus in a 47-year-old heavy cannabis user. A complete ophthalmic evaluation including visual acuity tests, intraocular pressure, fundoscopic examination, automated 10° central visual field, full-field electroretinogram (ERG) and multifocal ERG was performed twice – 30 min and 5 h after cannabis smoking. A strong decrease (up to 48%) in the a-wave amplitude of the full-field ERG was measured 30 min after cannabis smoking for all scotopic responses compared with the responses 5 h after smoking. Other tests showed reproducible results between the 2 series of measurements. This clinical case suggests that acute inhalation of cannabis affects the photoreceptors functioning. This rare situation suggests further investigations are required on the impact of cannabis on retinal processing, especially since cannabis has been incriminated in car injuries.

Introduction

While cannabis is very widespread worldwide, there is little information on its effects on human retinal processing. Numerous previous studies have shown visual symptoms or impairments in cannabis smokers and several have suggested a retinal origin (for review, see [1]). This hypothesis is consistent with the anatomical and functional distribution of the cannabinoid system in the retina (for reviews, see [1, 2]). Nevertheless, alterations in human retinal processing after acute cannabis use have, to our knowledge, not previously been reported whereas modifications of electrooculogram measurements, a marker of retinal pigment epithelium functioning, were

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found in several cannabis smokers [3, 4]. Here, we describe the first clinical case where decreases up to 48% in the a-wave amplitude of the full-field electroretinogram (ERG) measurements in scotopic conditions were found in a patient after an acute inhalation of cannabis. These strong alterations in retinal function were observed for all scotopic retinal responses and disappeared after the acute cannabis exposure phase. This observation may suggest a direct action of cannabis on the retina and therefore could provide a clearer picture of visual function in cannabis users.

Case Report

A 47-year-old man returned to the Ophthalmology Department for his annual monitoring examination in the context of a chloroquine treatment, prescribed for a systemic lupus erythematosus. The disease was revealed by erythematous edematous skin lesions located mainly on the cheeks and nose. These lesions were associated with rheumatological manifestations such as arthromyalgia and bilateral and symmetrical arthritis in the metacarpophalangeal and proximal interphalangeal joints. Biological cue for lupus erythematosus was an elevated level of anti-DNA native antibodies. The patient did not report visual impairment over the course of the disease. He had no history of ophthalmological, neurological or psychiatric disease. He was free of medication except for chloroquine. He had been taking chloroquine since 2003 and the total amount of chloroquine used at the time of the assessment was 1,000 g. Incidentally, he disclosed regular cannabis use associated with his tobacco consumption. He had started consuming cannabis 33 years ago. His cannabis consumption was estimated at approximately 20 joints of cannabis resin monthly. He smoked 40 tobacco cigarettes daily and had been doing so for 25 years. He denied any other current or past drug use. A standardized method using gas chromatography/mass spectrometry was used for analysis of urinary tetrahydrocannabinol (THC) and its main metabolites named 11-nor-9-carboxy-THC and 11-hydroxy-THC; buprenorphine; benzodiazepines; cocaine; opiates; amphetamines and methadone (Drug-Screen, Nal von Minden, Moers, Germany). This test was only positive to THC and its metabolites. To verify whether ophthalmologic measurements could be affected by his cannabis use, we agreed with him that he would come twice a day to perform an ophthalmic evaluation. The first one was performed 5 h after his last cannabis use. The patient then smoked again and the second evaluation took place 30 min after cannabis smoking. These tests included full-field ERG, according to the standards of the International Society for Clinical Electrophysiology of Vision [5]. Stimulation, recording and analysis were performed with MonPack One system and electrical signals were recorded simultaneously from both eyes using ERG-jet contact lens electrodes (Metrovision, France). Ground and reference electrodes were secured to the forehead and external canthi. Pupils were dilated with tropicamide 0.5%, and the pupillary size remained constant during the whole testing period. After periods of dark and light adaptation respectively of 20 and 10 min, full-field ERG was performed in both scotopic and photopic conditions. The following responses, named according to conditions of adaptation and flash strength in candelas seconds per meter squared, were recorded: light-adapted 3.0 and 3.0 flicker and dark-adapted 0.1, 0.3, 1.0 and 3.0 ERG. The recordings were performed in similar conditions 5 h after exposure and following acute cannabis exposure. Other tests included visual acuity tests, intraocular pressure, fundoscopic examination, automated 10° central visual field and multifocal ERG. The patient gave his consent to these explorations and for the publication of his case.

Results

We found that 30 min after smoking, the a-wave amplitude decreased by 48, 28, 23, 21% for the dark-adapted 0.1, 0.3, 1.0 and 3.0 ERG, respectively; compared to the responses 5 h after smoking. This decrease was found in all scotopic responses, was constant for both eyes and was not associated with subjective visual disturbances after cannabis use. Typical full-field ERG waveforms are presented in figure 1, showing reproducibility in the responses. Importantly, variations of ERG parameters derived from other retinal responses between the 2 measurements were substantially lower (table 1). Additionally, visual acuity tests, intraocular pressure, fundoscopic examination, central visual field and multifocal ERG were within normal limits and revealed no difference between the 2 measurement series.

Discussion

We have shown that the acute consumption of cannabis in our patient was followed by a large decrease in the a-wave amplitude for all scotopic responses, up to 48%, without subjective visual disturbance. To our knowledge, this is the first description of alterations in human photoreceptors functioning after acute cannabis smoking. This unusual and rare observation was favored by the need of an annual ophthalmic evaluation in a cannabis smoker, while clinical studies in cannabis users are difficult to perform due to numerous factors previously described [1]. These new findings could provide critical knowledge to the literature and could legitimize the development of case–control studies evaluating the retinal function in cannabis users.

These results suggest an acute and substantial effect of cannabis in modulating the hyperpolarization of photoreceptors. This is consistent with the distribution of endocannabinoids in the retina and with their role in the regulation of retinal neurotransmission (for reviews, see

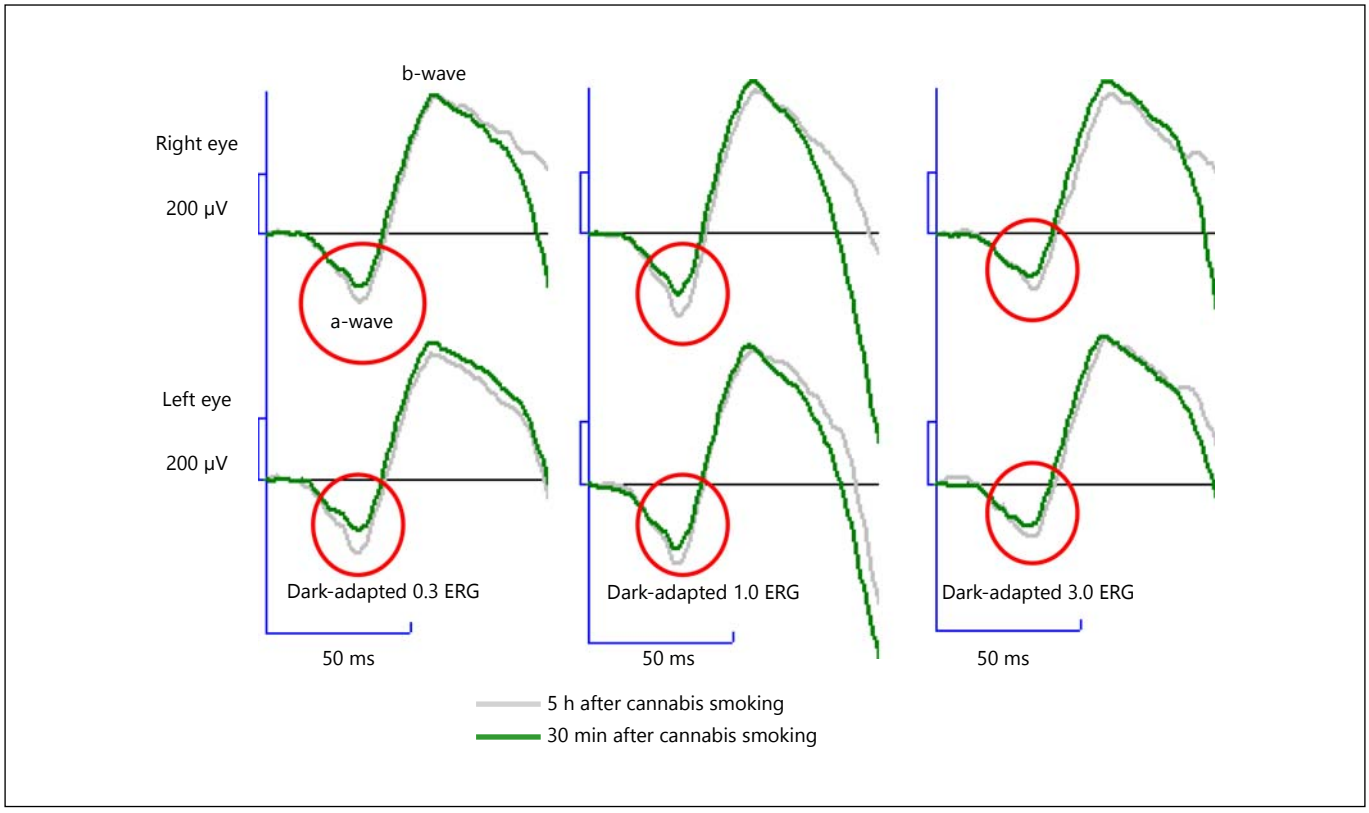

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Fig. 1. Typical full-field ERG traces in dark-adapted 0.3, 1.0 and 3.0 ERG conditions in an adult human 30 min and 5 h after cannabis smoking.

Table 1. Data of scotopic full-field ERG measurements in an adult human 30 min and 5 h after cannabis smoking

Mean right–left eye	Dark-adapted 0.1 ERG				Dark-adapted 0.3 ERG			
	a-wave		b-wave		a-wave		b-wave	
	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV
5 h after cannabis use	35.4	−95.4	67.3	512	31	−215.5	57.55	621.5
30 min after cannabis use	34.5	−49.2	70.85	472.5	31.45	−154.5	57.6	576.5
Percentage change, %	−3	−48	5	−8	1	−28	0	−7
Mean right–left eye	Dark-adapted 1.0 ERG				Dark-adapted 3.0 ERG			
	a-wave		b-wave		a-wave		b-wave	
	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV	implicit time, ms	amplitude, µV
5 h after cannabis use	30.55	−241	57.15	656.5	31.9	−159.5	59.75	587.5
30 min after cannabis use	29.65	−185.5	55.8	620	31	−126	59.3	574
Percentage change, %	−3	−23	−2	−6	−3	−21	−1	−2

[1, 2]). Cannabinoid receptors types 1 and 2 (CB1 and CB2) are expressed in the retina. An experimental study in CB2 knockout mice showed an increase in the a-wave amplitudes of the ERG measurements in scotopic conditions, also suggesting that cannabinoid receptors activation through cannabis would lead to a decrease in a-wave amplitudes [6].

Circadian variations are unlikely to have played a role in these responses variations, because they would have led to variations in other scotopic parameters also, which was not the case. Similarly, tobacco is unlikely to be involved, since nicotine is known to decrease the scotopic b-wave amplitude [7].

The retina is an anatomical and functional extension of the central nervous system (CNS). As a consequence, the retina and the brain display similar properties, especially in terms of neurotransmission [8]. In this context, multiple studies suggest that retinal function could be affected in CNS disorders involving neurotransmission abnormalities [9–12]. Cannabis is known to act on CNS neurotransmission, especially on glutamatergic, dopaminergic, and GABAergic pathways [13]. These neurotransmitters are expressed in the retina and are involved in several physiological conditions [14, 15]. We hypothesize that our findings could support a direct action of THC on retinal glutamatergic transmission. Indeed, one of the crucial functions of the cannabinoid system is the inhibition of neurotransmitters release, which is allowed by the location of CB1 receptors at the presynaptic level of central and peripheral neurons, such as in the retina [1, 2]. As previously described in the CNS, the blockade of pre-synaptic CB1 receptors by THC disrupts the regulatory role of endocannabinoids and consequently increases the synaptic release of glutamate (for reviews see [1, 13]). This leads to alterations in synaptic glutamatergic transmission. In the vertebrate retina, glutamate is expressed in the main retinal cells, such as photoreceptors [14, 16]. Furthermore, glutamate is the main neurotransmitter involved in the depolarization and hyperpolarization of photoreceptor cells and consequently in the vertical transmission of retinal information [14, 16]. Based on our results, we propose that cannabis use, through the direct action of THC on retinal cannabinoid receptors CB1, modulates the retinal level of glutamate thus altering the hyperpolarization of photoreceptor cells.

An impact of the immune disease, lupus erythematosus, and chloroquine intake in these transient alterations of photoreceptors functioning is unlikely for the following reasons, although we cannot exclude an interaction with cannabis intake. Our patient did not have subjective visual disturbances at the time of the assessment and had not reported any visual impairment since the disease was diagnosed. The transient retinal dysfunctions were reported after acute cannabis smoking and disappeared at a distance from cannabis use, suggesting a direct and independent effect of cannabis use. These results cannot be related to chloroquine intake since annual ophthalmological monitoring was performed to verify potential toxicity of chloroquine intake on retinal function; these exams, including multi-focal ERG recordings, were within normal limits and were stable and reproducible between each annual monitoring.

However, the modulation of immunoregulatory effects of cannabinoid signaling through an action of THC on the cannabinoid system could be considered in retinal dysfunctions occurring in this specific immunological pathological condition. Indeed, cannabinoid receptors and their endogenous ligands are found in cells of the immune system both in peripheral tissues and in the CNS [17]. Additionally, there is growing evidence that cannabis and exocannabinoids exhibit immunoregulatory properties through the activation of cannabinoid receptors [17, 18]. Especially, endocannabinoids are known to exert immune functions by modulating cytokine release and an involvement of the cannabinoid system in a protective general mechanism may occur in specific immunological conditions to decrease the immune response [19, 20]. Under pathological conditions such as lupus erythematosus, the expression of cannabinoid receptors may be enhanced and they could play neuroprotective and immunosuppressive roles [21]. As a consequence, the retinal dysfunction recorded after cannabis smoking could also result from interactions between the cannabis effect and special immunological disease mechanisms of lupus erythematosus, resulting in modulation of the role of the cannabinoid system.

Cannabis is widespread worldwide and its use might be associated with impairments in vision, critical for car driving. Because data on the visual impact of acute cannabis exposure are still limited, this case indicates a need for further clinical investigations on visual function in cannabis users.

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Disclosure Statement

The authors declare that they have no conflict of interest.

Contributors

All the authors contributed to write the manuscript, concurred with the submission and have approved the final manuscript.

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