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ORIGINAL RESEARCH ARTICLE

Ophthalmological assessment of cannabis-induced persisting perception disorder: Is there a direct retinal effect?

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Abstract
Purpose Cannabis is a psychotomimetic agent that induces impairment of sensory perception. We present detailed clinical and electrophysiological data of patients with hallucinogen persisting perception disorder (HPPD) after marijuana consumption.
Methods A HPPD patient and four heavy cannabis smokers with no visual disturbances (controls) underwent complete ophthalmological examination including psychophysical tests (visual acuity, color vision, visual field, and dark adaptation) and detailed electrophysiological examinations, including extended Ganzfeld ERG, multifocal ERG, and electrooculography (EOG). Furthermore, electrically evoked phosphene thresholds (EPTs) were measured to further evaluate retinal function.
Results Ophthalmological and most electrophysiological examinations were within normal limits for the HPPD patient and for all control subjects. Interestingly, EOG results of the HPPD patient showed a slightly reduced fast oscillation ratio, diminished standing potentials of the slow oscillations, and a light peak within normal range resulting in higher Arden ratios. The EPTs of the patient were reduced, in particular for pulses with long durations (50 ms) causing visual sensations even at lowest possible currents of the neurostimulator. The control subjects did not reveal such alterations.
Conclusions Our findings suggest a direct effect of cannabinoids on the retina and retinal pigment epithelium function, which may be involved in disturbances of the visual function experienced after drug consumption. The observations presented here may contribute to the elucidation of the detailed mechanism. Furthermore, EOG and EPT measurements may be useful tools to demonstrate long-term retinal alterations in cannabis-induced HPPD in patients.

Keywords Electrophysiology · Persisting perceptual disorder · Cannabinoid receptors · Retina

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Introduction

Hallucinogen persisting perception disorder (HPPD) is a temporary recurrence of disturbances in perception that are reminiscent of those experienced during one or more earlier intoxications with hallucinogens and includes many types of visual disturbances [1–13]. These perceptual changes can be halos around objects, difficulty in distinguishing between colors, alterations in color perception, geometric hallucinations, illusions that objects are moving or changing in size, "visual snow," or floaters [8, 9]. Some of these visual phenomena (e.g., floaters and afterimages) occur even in healthy subjects, who have never taken drugs [7], which makes the identification of HPPD difficult. Furthermore, the probability of developing HPPD after consuming a hallucinogen and its true prevalence are unknown, and the upper limit probably does not exceed 0.66 % according to literature [8].

Currently, although no effective treatment against these symptoms is available, some medications like diazepam or alprazolam seem to be helpful [11, 12]. It is generally recommended that patients should discontinue taking drugs and should also avoid caffeine and alcohol, which might have a negative effect on HPPD [13]. In most of the cases, HPPD disappears spontaneously, but the duration can vary between individuals: Some patients have symptoms for months, but these can also last for years [5, 13]. Disturbances of visual perception following drug consumption are often unexplained, or symptoms can be misinterpreted [14].

Tetrahydrocannabinol (THC, marijuana, cannabis) is a psychotomimetic agent that induces impairment of sensory perception [1–4]. Although short-term effects on the visual system are well known [4], there is only little information on persisting visual disturbances [5, 6].

The activation of the cannabinoid receptors CB1 and CB2 in the visual cortex is certainly associated with the occurrence of perceptual changes [15, 16]. Nevertheless, there is evidence that direct activation of cannabinoid (CB) receptors in the retina can also play an essential role, since CB1 receptors have been found to be present in the retina as well [17, 18].

The activation of CB receptors has been associated with functional alterations in the three major retinal neurons: CB receptors were shown to reduce cyclic adenosine monophosphate (cAMP), which modulates voltage-dependent currents of cones [19], and therefore, they are suggested to modulate neurotransmitter release at the first synapse of the visual system [20]. A reciprocal inhibition of voltage-gated potassium currents by activation of cannabinoid CB1 in ON bipolar cells of goldfish retina has been reported [21], and at last, CBs can modify the excitability of retinal ganglion cells (RGC) [22]. All together, CBs might be able to mimic the light activation of photoreceptors, and therefore, CB1 and possibly CB2 expression may explain some of the CB-induced visual effects. Furthermore, the presence of CB receptors in human retinal pigment epithelium (RPE) has also been demonstrated [23, 24].

Some case reports mention normal retinal function in patients with HPPD [5, 6]; however, in none of them an extended electrophysiological evaluation was carried out. We hereby report detailed results observed in a patient, who claimed of cannabis-induced persisting perception disorder even after long period of marijuana abstinence. The results are compared with the findings of four heavy cannabis smokers without visual disturbances, serving as controls, and with our normative database.

Subjects

The research followed the tenets of the declaration of Helsinki, and the study was approved by the Ethics Committee of the University of Tübingen, Germany. Normal and control subjects were derived from the faculty, staff, and student body of the University, and the participating patient was recruited from the Department of Ophthalmology, University of Tübingen, Germany. All participants were included in the study after written informed consent. None of the subjects had suffered from psychotic symptoms or hallucinations before.

Patient

A 23-year-old male student complained of visual changes lasting for several years. He started smoking marijuana and cigarettes heavily at the age of 16 years. This period lasted uninterruptedly for about 4 years. Besides marijuana, he denied using any other drugs. He developed a persistent perception disorder despite discontinuing the use of cannabis a few months after the onset of his persistent visual symptoms. These included perception of visual snow, sperm-like

whizzing dots, jittering lights, floaters, photophobia and visual discomfort, increased positive and negative afterimages, impaired night vision, increased halos, and starbursts around lights. These symptoms were so annoying that he could not follow the lectures at the university. Besides a slightly elevated blood pressure, the clinical and neurological examinations including MRI did not reveal any altered result.

Controls

We recruited four young control subjects (one female, three male, mean age 25.5 years, range between 23 and 28 years) from our university, who considered themselves as heavy cannabis smokers, but denied any visual disturbances. The controls were otherwise healthy and had normal ophthalmological findings. Other drugs were not consumed.

Methods

A complete ophthalmological examination was carried out, including Snellen visual acuity, pupil reaction, Lanthony Panel D-15 color vision test, dark adaptation, visual field, and an extended electrophysiological examination.

Ganzfeld and multifocal ERGs were recorded according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [25, 26], but additional stimuli were included to improve retinal function evaluation. All tests were performed using DTL electrodes with an Espion E^2 (Diagnosys LLC) recording device coupled with a ColorDome (Diagnosys LLC) as light source. After 30 min of dark adaptation, a series of responses to increasing flash intensities (4 ms—0.0001–10 cd.s/m^2 in 0.5 log unit steps) were recorded, and the stimulus–response (S–R) functions modeled using the equation:

$$V(I) = V_{\max} \times I^n/(I^n + K^n)$$

with the saturated b-wave amplitude $V_{\max}$, the flash intensity K required for semi-saturation as a measure of retinal sensitivity, and the slope related exponent n [27].

With a question in mind, that the marijuana-induced alteration in CB receptor function may affect photoreceptor-RPE interaction, dark-adapted responses to a series of blue flicker (LED 470 nm) with an intensity of 0.03 cd.s/m^2 and frequencies between 5 and 30 Hz were recorded.

The light-adapted protocol (10 min of light adaptation to a background luminance of 30 cd/m^2) included a single flash cone stimulus, ON–OFF measurements, and 30 Hz flicker (both: 4 ms, 3.0 cd.s/m^2). In addition, responses to a flicker series with white stimuli of 3.0 cd.s/m^2 with increasing frequency from 5 to 45 Hz were included to investigate possible alterations in the temporal resolution of the cone retinal pathway.

Multifocal ERG (mfERG) was performed with a VERIS System (Version 5.1) using a Grass amplifier (model 12, Quincy, MA, USA) or with an Espion System (Diagnosys LLC). The stimulus, consisting of 61 scaled hexagonal elements covering a central visual field of 60 × 55°, was presented on a 19″ monitor at a frame rate of 75 Hz at a distance of 32 cm from the subjects' eyes. Responses were amplified (200 000x), bandpass filtered (10–100 Hz), and analyzed according to ring averages.

Electrooculography (EOG) measurements were recorded with either the Tübinger EOG device or with the Espion E^2 (Diagnosys LLC) recording device coupled with a ColorDome (Diagnosys LLC) as light source in the controls according to the standards of ISCEV [28]. A fast oscillations protocol was included to extend functional evaluation of the RPE. The use of the two different devices was necessary due to modernization of the electrophysiology lab, but measurement protocols were identical. Normal values were available for both devices, and results were compared with the appropriate data.

To test retinal sensitivity to electric stimulation, phosphenes were elicited by using a neurostimulator (Twister; Dr. Langer GmbH, Waldkirch, Germany) by means of DTL electrode as active electrode and a gold-plated cup electrode on the temporal skin connected to the negative pole. The neurostimulator was modified by the manufacturer to scale down current output. Impedance of the electrodes was tested using the built-in algorithm and at no time exceeded 5 kΩ. Measurements were performed in the dark; light was switched on periodically in order to avoid dark adaptation. Full darkness was necessary to perceive the very subtle phosphenes. A four-alternative forced-choice method was used for psychophysical determination of electrically evoked phosphene thresholds (EPT) in series of "biphasic positive" rectangular

current pulses with duration of 1.0, 5.0, 25.0, and 50.0 ms [29].

Retrieved data were compared with the normal values obtained in the Centre for Ophthalmology—University of Tübingen Germany under standard conditions. The statistical analysis of the data was conducted by using the JMP 10 statistical software (SAS Institute Cary, North Carolina, USA).

Results

Patient

The ophthalmological examinations revealed hyperopia, although the patient had never needed glasses before. Best-corrected visual acuity was 1.25 (Snellen) on both eyes (RE: +2.0 sph −0.25 cyl 95°; LE: +1.75 sph −0.25 cyl 115°). The range of accommodation was six diopters on both eyes. Neuroophthalmic examinations, color vision tests, and dark adaptation thresholds did not show any abnormalities. No relative afferent pupillary defect (RAPD) has been observed. Anterior segment and fundus appearance were completely normal, and intraocular pressure was 10 mmHg in both eyes.

Ganzfeld dark- and light-adapted ERG responses a- and b-wave amplitude and implicit times, oscillatory potentials and parameters V_{max} and k, light-adapted responses, single flash cone, ON–OFF responses, and all flicker frequencies were within normal ranges in both eyes (Fig. 1). Multifocal ERG response amplitudes and implicit times were also normal.

The EOG showed a slightly reduced fast oscillations ratio (FO ratio = 1.08 and 1.15 on right and left eyes, respectively), and the slow oscillations EOG showed diminished trough standing potentials (6.0 and 6.45 μV/deg in the trough before onset of light) with a peak within the norm values (23.79 and 19.16 μV/deg) with Arden ratios of 3.967 and 2.97, respectively (Table 1; Fig. 2).

The phosphene thresholds were considerably reduced (Table 2; Fig. 3), i.e., the patient needed less current to cause phosphene sensations in both eyes, in particular for pulses with long durations (50 ms) where the subject could refer visual sensations even by the minimal current that can be produced with the neuro-stimulator (0.001 mA).

Controls

Best-corrected visual acuity was 1.0 (Snellen) in the control subjects, and visual field tests showed normal results. Neuroophthalmic examinations, color vision tests, and dark adaptation thresholds were within normal limits. No RAPD was detected. Anterior segment and fundus appearance were completely normal, and intraocular pressure was within normal limits in every case. Ganzfeld and multifocal ERGs were not altered (Fig. 1), and EPT measurements were also normal (Table 2; Fig. 3). The EOG measurements showed baseline values in the upper normal values of the fast oscillations in every control subject, and other parameters were inconspicuous.

Discussion

Different cannabis products, marijuana and hashish (concentrated form), are considered to be natural hallucinogens and are derived from the hemp plant (Cannabis sativa). Marijuana, a green herb from the flower, is considered a mild hallucinogen in comparison, for example, with LSD. Both drugs are usually smoked, and their effects include a feeling of relaxation, faster heart rate, the sensation that time is passing more slowly, and augmented sensory experiences concerning hearing, taste, touch, and smell.

Epidemiological studies show that marijuana is still a widely used illicit drug particularly in youth in many countries, and during the past decades, there is a growing interest on its potential side effects [30–33].

While the acute and short-lasting effects are relatively well described, questions and controversy remain on possible chronic and long-term effects. HPPD has been relatively well described for LSD [1, 10–12, 34], but it is not clearly known, whether cannabis can also provoke it. Diagnosis of cannabis-induced HPPD may be considered in rare cases following a full diagnostic workup to exclude other disorders, such as temporal lobe epilepsy or cortical tumor, presence of systemic disorders with cerebral effects, such as systemic lupus erythematosus, head trauma, intraocular pathology, and multiple sclerosis, or the use/interruption of other concomitant drugs or toxic exposures (heavy metals, insecticides, other aerosolized hydrocarbons, arsenic, and bromism) [4–6, 34].

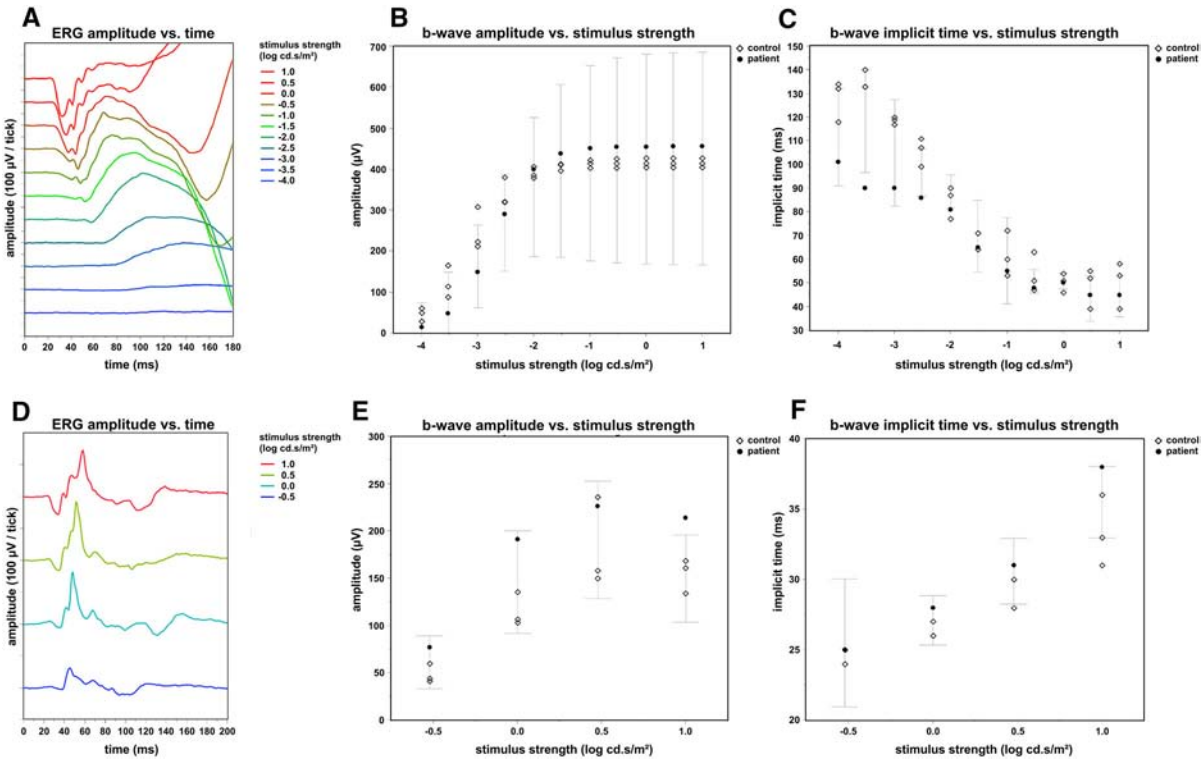

Fig. 1 Ganzfeld ERG results. The scotopic (**a**) and photopic (**d**) ERG responses of the patient to increasing stimulus intensities showed normal waveforms. Scotopic b-wave amplitudes (**b**) and implicit times (**c**) were within normal limits for the patient and for all control subjects, such as amplitudes (**e**) and implicit times (**f**) of the photopic responses. The *bars* indicate the normal range, the *filled circles* represent results of the patient, and the *diamonds* represent results of the controls measured ($n = 3$)

Table 1 EOG results of the patient

	OD	OS	Normal range	
			N 5 % quantile	N 95 % quantile
Fast oscillation max. (µV/deg)	11.93	12.84		
Fast oscillation min. (µV/deg)	11.01	11.14		
Fast oscillation ratio	1.083[a]	1.152[a]	1.18	1.48
Slow oscillation (Arden)	3.967[a]	2.97	2.08	3.0
Peak (µV/deg)	23.79	19.16[a]	20.6	45.1
Trough (µV/deg)	6.0[a]	6.45[a]	9.2	19.2

The EOG showed slightly reduced fast oscillations ratios, and the slow oscillations showed diminished trough standing potentials with nearly normal peak values, resulting in higher Arden ratios for both eyes. The four control subjects were all within normal limits. The absolute values of the peak and trough standing potentials (in µV) can be calculated by multiplying the peak and trough values (given in µV/deg in the table) with 30 degrees, in accordance with the ISCEV Standards

N = normal, OD = right eye, and OS = left eye

[a] Pathologic result

The patient presented here did not show any systemic or ocular disorder, and as previously described in other reports [5], our standard ophthalmological examinations did not reveal any functional or morphological ocular alteration either. Responses in Ganzfeld and mfERG were also within normal limits, and therefore, it seems

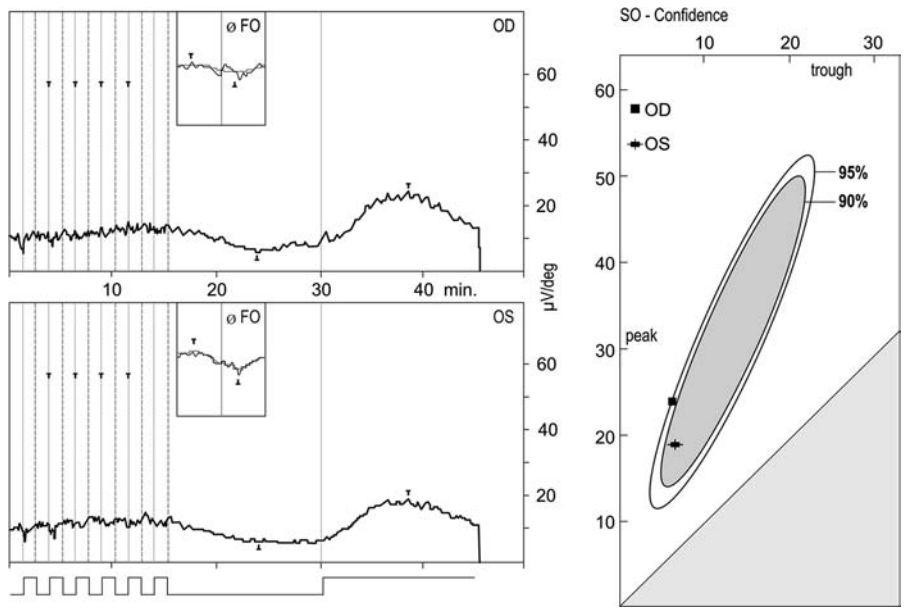

Fig. 2 EOG results of the patient. While fast oscillations (FO) were reduced, slow oscillation (SO) ratios were rather above the normal limit due to reduced trough standing potentials and a peak within the norm values

Table 2 Electrically evoked phosphene threshold (EPT) results of the patient and control subjects

Pulse duration (ms)	Threshold (mA)						
	P1 OD/OS	C1 OD/OS	C2 OD/OS	C3 OD/OS	C4	N 5 % quantile	N 95 % quantile
1	0.2/0.3	0.05/0.07	0.2/0.55	0.2/0.02[a]	n.a.	0.1	0.55
5	0.01[a]/0.02	0.07/0.2	0.14/0.18	0.02/0.02	n.a.	0.02	0.15
25	<0.0001[a]/0.0005[a]	0.1/0.07	0.036/0.055	0.026/0.03	n.a.	0.01	0.1
50	<0.0001 OU[a]	0.08/0.07	0.06/0.06	0.007[a]/0.018	n.a.	0.01	0.1

The EPTs of the patient were reduced, in particular for pulses with long durations (50 ms) causing visual sensations even at lowest possible currents of the neurostimulator. The control subjects did not reveal such alterations

n.a. = not available, N = normal, OD = right eye, OS = left eye, and OU = both eyes

[a] Pathologic result

reasonable to assume that the systems that are mostly responsible for the ERG response generation (phototransduction and postreceptoral signaling) in both rod and cone pathways are physiologically normal.

Surprisingly, alterations in two other electrophysiological examinations did show up. We observed a massive reduction of phosphene rheobase, when measuring the threshold current required to elicit visual sensation. Although there is ongoing debate on the exact site of electrical stimulation within the retina and some have argued that the photoreceptors are preferentially driven, evidence is emerging that photoreceptors and their synapses to bipolar cells are the preferential target because even retinas without any functioning photoreceptors can be stimulated within reasonable thresholds [29]. We know that CB1 receptor is expressed at the pre-synaptic site, where it inhibits voltage-gated Ca^{2+} channels and thus reduces the pre-synaptic neurotransmitter release, indicating that this receptor is an important regulator of synaptic transmission in the retina [35]. The markedly increased sensitivity to electrically evoked phosphenes in cannabis-induced HPPD suggests altered mechanisms of the signal transmission in the retina that may cause hyperexcitability, e.g., in response to the permanently ongoing spontaneous

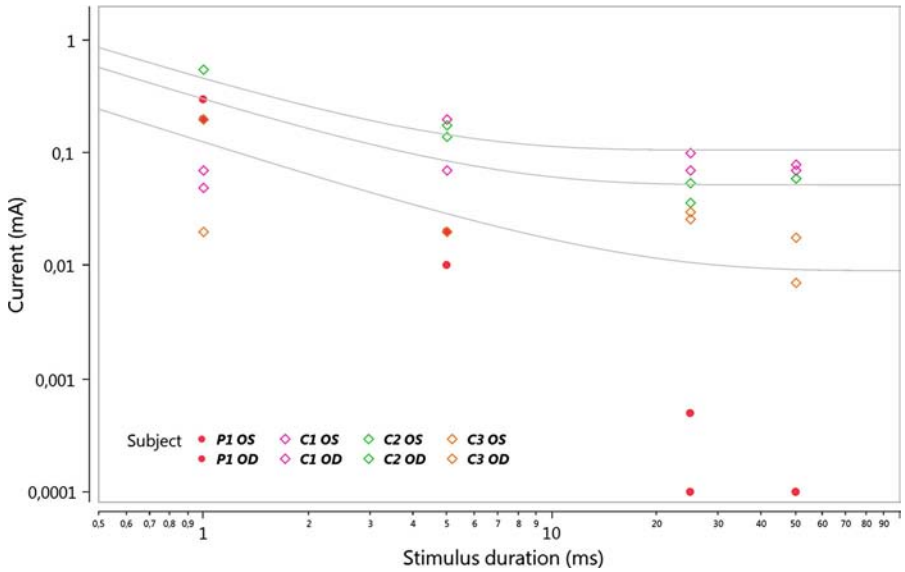

Fig. 3 Strength–duration curve in a double-logarithmic representation of electrically evoked phosphene thresholds (EPT). We observed a massive reduction of phosphene rheobase in the patient, when measuring the threshold current required to elicit visual sensation. Control subjects—who denied any visual disturbances—showed normal EPT results. *Red filled circles* represent the EPT values of the patient, and empty diamonds (*pink*, *green,* and *orange*) show results of the control subjects

activity of neurons in the retina. A further alternative could be a reduced outer blood retinal barrier integrity that may account for the phosphenes being visible at low currents. Taken the RPE's resistance is low, the current could trigger bipolar cell activity more easily as the resistive path to the outer retina is reduced. Moreover, psychophysical examination involving central visual processing might also be associated with specific psychophysiological responses, since long-term heavy cannabis users show changes both in cortical and peripheral reactivity [36–38]. Therefore, a direct effect of CBs on the retinal function is suggested to be involved in disturbances of the visual function experienced after drug consumption.

Further, clinically measurable alterations were observed in the EOG. We reported reduced trough standing potentials and reduced fast oscillations ratios in the patient. The EOG is an electrophysiological test of function of the outer retina and RPE in which the change in the electrical potential between the cornea and the ocular fundus is recorded during successive periods of dark and light adaptation. This potential is mainly generated by the RPE and depends on the ion permeability across its basal membrane [28]. So far, several different ion channel types have been suggested to be involved in the generation of these potentials: Cl^- channels and L-type channels of the neuroendocrine subtype seem to have an important role [28, 39]. Changes in the EOG in Best's disease caused by alterations of bestrophin-1, a Cl- channel, indicate the involvement of Cl^- channel in the EOG [39]. Mice deficient of neuroendocrine L-type channels show reduced standing potential in direct measurements. Recently, Wei et al. [23] showed the presence of CB1 and CB2 receptors in human RPE cells, suggesting a key role for the endocannabinoid system in neurodegenerative disorders. As the RPE expresses both cannabinoid receptors, it is likely that the observed changes are due to cannabinoid-dependent modulation of the ion channels in the RPE. CB1 receptor is known to modulate different ion channels: such as inhibition of L-type channels [40] or activation of TRPV1 and TRPV2 cation channels [41]. L-type channels [42] and TRPV1 and TRPV2 channels are expressed by the RPE. In the RPE, it has been shown that cannabidiol leads to increase in intracellular free Ca^{2+} though activation of TRPV2 channels [24]. Thus, it is possible that acute stimulation of the RPE by reminiscent CB receptor agonists or their metabolites could be responsible for the observed changes by an increase in intracellular free Ca^{2+} which in turn can lead to activation of ion channels such

Ca^{2+}-dependent Cl^- channels in the basolateral membrane. Activation of Ca^{2+}-dependent Cl^- channels in turn is known to generate the increased basolateral Cl^- conductance which is the base for the light rise in the EOG [43]. This might explain the observed changes in the EOG. In addition to this acute effect, sustained effects are also likely to be responsible for the observation. There are several reports about long-term effects of prolonged stimulation by CBs in the neuronal system [44], which may be explained with changed ion channel gene expression dependent on modulation of Ca^{2+} channel activity. It should be noted that also stimulation of CB1 leads to an increased surface expression of TRPV2 channels, which would generate a long-term effect [45]. We presume that due to CB receptor overstimulation the basolateral membrane shows a lower Ca^{2+}-dependent Cl^- conductance, probably due to decreased L-type channel activity causing lower basal Ca^{2+} levels. This in turn decreases the activity of Ca^{2+}-dependent Cl^- channels and conductance for Cl^- of the basolateral membrane, which would explain in part the reduced standing potential and the reduced FO, since the same change in intracellular Cl^- in the RPE would result in less hyperpolarization of the basolateral membrane. Thus, we believe not in a direct contribution of Ca^{2+} in the generation of the FO but a changed generation of the FO due to less basal Ca^{2+}-dependent conductance of the basolateral membrane.

Another possible explanation for a reduced standing potential in the EOG could be a reduced resistance between the basal and apical membranes. The RPE cells are connected by tight junctions, so the resistance across the layer is quite high. These tight junctions are regulated by Ca^{2+} and Ca^{2+} homeostasis. Should Ca^{2+} homeostasis in cannabis users be abnormal, the reduced standing potential could also be explained by a reduced resistance between the basal and apical membranes. Alternatively, should tight junctions be not affected, reduced FOs could occur, if the apical voltage would be approximately equal to the basal voltage with the consequence that there would be less shunt current to develop the light trough of the FOs.

Thus, the observed changes in the EOG might be related to a different ion channel expression profile in the RPE of the patients, which could also explain why the EOG results of control subjects were within normal limits and why there are limited studies on cannabis-induced HPPD despite its widespread use. In some cases, HPPD appears to have a sudden onset after a single drug experience, strongly suggesting the drug played a direct role in triggering symptoms. But in other cases, people report gradual worsening of symptoms with ongoing drug use. It is possible that the prevalence of HPPD is underestimated by authorities because many people with visual problems relating to drug use either do not seek treatment or, when they do seek treatment, do not admit having used illicit drugs. Thus, it may be that HPPD occurs more often than is detected by the health care system.

However, the exact chain of events, possibly at multiple sites (retinal as well as cerebral) in cannabis-induced HPPD, remains unexplained. The observations presented here in relation to electrophysiological events as well as in relation to Cl^- channels may contribute to the elucidation of the detailed mechanism. Up to now, there are no randomized controlled trials to investigate visual function or test treatment possibilities against HPPD regardless the hallucinogenic drug that caused it. EOG and EPT measurements could be useful tools to demonstrate retinal alterations in cannabis-induced HPPD.

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