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Different Effects of Nabilone and Cannabidiol on Binocular Depth Inversion in Man

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LEWEKE, F. M., U. SCHNEIDER, M. RADWAN, E. SCHMIDT AND H. M. EMRICH. *Different effects of nabilone and cannabidiol on binocular depth inversion in man*. PHARMACOL BIOCHEM BEHAV **66**(1) 175–181, 2000.—The physiological and pathophysiological roles of the central nervous endogenous cannabinoid system are not completely understood, but still represent a challenge in basic neurobiological, cognitive, and psychiatric research. The system has been implicated in the pathogenesis of schizophrenia. Binocular depth inversion, an illusion of visual perception, provides a model of impaired perception during psychotic states. Using this model the effects of nabilone, a psychoactive synthetic 9-trans-keto-cannabinoid, and of cannabidiol, the main natural component of herbal cannabis, and a combined application of both substances on binocular depth inversion and behavioural states were investigated in nine healthy male volunteers. The time course of the effects of both substances on binocular depth inversion was analysed after oral administration using three different groups of natural stimuli. A significant impairment of binocular depth perception was found when nabilone was administered, but combined application with cannabidiol revealed somewhat reduced effects on binocular depth inversion. The influence of psychoactive cannabinoids on this perceptual model and the role of the endogenous cannabinoid system in visual information processing are discussed. © 2000 Elsevier Science Inc.

Cannabinoids Cannabidiol Nabilone Binocular depth inversion Humans

VARIOUS effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) have been investigated over the last decades since it has been identified as the major psychoactive compound of cannabis resin (11). The recent identification of a central nervous cannabinoid receptor (4) and of the first endogenous cannabinoid receptor ligands, anandamide and 2-arachidonylglycerol (5,39), gave rise to investigations of the specific actions of naturally and synthetically obtained cannabinoids [for review see (20)]. Previous studies on the effects of cannabis on visual perception in man mainly used cannabis resin with specified concentrations of Δ^9-THC. However, from a psychopharmacological point of view, the effects and interactions of synthetic and natural cannabinoid compounds with respect to visual perception and higher cognitive function are not completely understood. The administration of a not well-defined mixture of different genuine cannabinoids may cause a variety of neuropsychological effects that may not necessarily be associated only with the action of Δ^9-THC but show a complex pharmacology (30). Furthermore, the physiological and pathophysiological role of the endogenous cannabinoid system in humans remains widely unknown. However, there is clinical and experimental evidence for an implication of this system in the pathogenesis of psychoses (7,24,31).

Binocular depth inversion is a well-known model of illusionary perception. Binocular depth perception is influenced by various factors (29,32). Out of those, binocular disparity has been shown to be the most influential (42). Interchanging the view of the left and right eye using a stereoscope leads to a reversed depth experience of most objects ("pseudoscopic vision") (43). Under certain circumstances the individual perception of a pseudoscopically presented three-dimensional object may differ from the physical information of an object (veridical view). Today, visual perception is understood as an interaction of bottom-up and top-down processing resulting in the conscious experience of an object. A process of generating hypotheses about the three-dimensional shape of objects is thought to be basic for binocular depth inversion. In this process, the visual infor-

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mation from the eyes (bottom-up) is interpreted using conceptual and perceptual knowledge (top-down) as well as general rules of perception, such as Gestalt laws of organisation and perspective (13,16,45). Based on this concept, binocular depth inversion results from a domination of top-down processing of the presented objects (6,36). Thus, a reduction or reversal of binocular depth inversion by psychotropic cannabinoids would be due to an impairment of top-down processing. A reversal of this effect by additional administration of the nonpsychotropic cannabidiol might point to a putative effect of this natural cannabinoid in this model of impaired visual perception.

It has been shown that binocular depth inversion is significantly altered in patients with acute productive schizophrenic psychosis (36). Furthermore, we recently reported on the effects of synthetic Δ^9-THC on binocular depth inversion (25). Our interest now was in the effects of other psychotropic cannabinoid compounds on this paradigm. Based on our previous findings, we tested the hypothesis that binocular depth inversion is altered by psychotropic cannabinoids but not by nonpsychotropic cannabinoid compounds like cannabidiol. Moreover, we were interested in the effect of a combined administration of both substances to get some insight into their clinical interactions.

We, therefore, selected the synthetic Δ^9-THC-analogon, nabilone (CESAMET™), which has been approved for medical purposes in Germany (1983), and cannabidiol to study the effects and interactions of cannabimimetic compounds on binocular depth inversion. Nabilone reveals psychotropic effects that are very similar to Δ^9-THC (23). Furthermore, nabilone appears to act like an anxiolytic (9), and reveals relaxant and sedative effects at doses of 15 to 30 μg/kg body weight as well as dose-dependent euphoria in humans (23). Although cannabidiol has been found to have anxiolytic effects as well (49), cannabidiol is generally considered to be a neutral nonpsychoactive cannabinoid (18).

Recently, it has been proposed that cannabidiol has antipsychotic properties both in animal models predictive of antipsychotic activity and in humans (47,48). We used a single dosage of 200 mg cannabidiol. This dose is comparable to the dosage used in previous studies on the effects and clinical use of cannabidiol in humans (2).

METHODS

The local ethics committee approved the basic study protocol as outlined below. Nine healthy Caucasian males participated in the study. All were trained physicians, or in one case, a psychologist. The study was designed as a series of self experiments of trained professionals according to the Declaration of Helsinki. They signed an informed consent form, and were allowed to withdraw from the study at any time without disclosure of their reasons. The subjects were aged between 26 and 35 years, with a mean age of 29.4 years. All subjects reported normal health as well as normal or corrected-to-normal vision. Stereoscopic vision was tested using the Randot stereotests (Stereo Optical Co., Chicago, IL). Only subjects showing unrestricted binocular depth perception in this commercially available standard tests were included in the study. Subjects with a positive history of recurrent abuse of drugs other than cannabinoids, psychiatric, neurological, or medical diseases or a positive history of consumption of opiates, cocaine, amphetamines, or phencyclidine were not allowed to participate in this series of self-experiments. They were also excluded if they had consumed cannabinoids more than 10 times in their lifetime so as to rule out any influence from prior long-term cannabis use. No medication was allowed for at least 10 days before participation in the study.

Experiments took place on 3 days with an interval of 8 days between the different stages of the experiment. On each day, all subjects received a standardised breakfast 1 h prior to the start of the experiments. Afterwards, they performed baseline tests for binocular illusionary perception as well as behavioural measures as described below.

All substances were administered orally. Purified natural cannabidiol was generously supplied by Professor Raphael Mechoulam (Israel), nabilone (CESAMET™) was commercially acquired (Eli Lilly Company, Ltd.). On the first day of the study, cannabidiol (200 mg) was given with an additional placebo capsule resembling the nabilone capsule. On the second day of the study, cannabidiol (200 mg) and nabilone (1 mg) were administered. Finally, on the third day nabilone (1 mg) was given together with another placebo capsule resembling the cannabidiol capsule. The volunteers as well as the investigators were informed that two different cannabinoids were applied, but were blind to the order of administration and pairing of the capsules.

The experimental technique for testing binocular depth inversion has been described in detail elsewhere (25). Stereoscopic pictures from three groups of different natural objects—flowers, ordinary objects such as a chair, and faces of male, middle-age persons—were presented. Faces were photographed as frontal views, half of which were presented right way up and half presented upside down. Depth information of the pictures was manipulated by exchanging the left and the right picture taken, thus resulting in a change in disparity indicating an inverted object ("pseudoscopic vision"). The corresponding pictures were presented on a computer monitor with high resolution and color depth (16 bits) for a maximum of 60 seconds. A Wheatstone stereoscope (42) was used to achieve stereoscopic vision.

The volunteers were instructed that depth perception of each object might vary or not. They described their visual perception of each object using an operationalised description coupled with a five-step rating scale. When depth perception was totally inverted, zero points were given. Complete matching between depth perception and the physical information of an object was rated four points. On each occasion, two objects from each class were presented, and the ratings were averaged and divided through the maximum possible score. Thus, a maximum of one point was applicable for each class of objects. This score is referred to as an "inversion score."

Behavioural measures were performed on each day of the experiment. The general subjective mood was investigated using the Adjective Mood Scale [Bf-S, (46)], while the vividness of imagery was tested by use of the Bett's Questionnaire upon Mental Imagery [QMI; (37)]. Additionally, the effects of both substances on anxiety was repeatedly measured by use of the State-Trait-Anxiety-Inventory [STAI X1; (38)]. All three of these measures were completed prior to, 3 h, and 24 h after administration of the respective substances. The Self-Rating Anxiety-Scale [SAS, (50)] was also used on each experimental day 2.5 h after administration of the compounds.

Statistical analysis of the data was performed using SPSS™ (Statistical Package for the Social Sciences). A Friedman two-way ANOVA was used for analysing group effects. Subsequently, paired Wilcoxon-tests were performed where applicable.

RESULTS

General Observations

Most of the volunteers were able to tell if they had received a psychoactive cannabinoid. In general, clinical experience of nabilone intoxication was slightly reduced when administered along with cannabidiol. Cannabidiol itself produced some sedative effects, but was not found to match previous cannabinoid experience in our volunteers. Nabilone induced relaxant and mild sedative effects in all subjects. Three volunteers described very mild euphoria. All volunteers described negative effects on concentration, which were noticed most intensely during the experimental condition.

Behavioural Measures

The behavioural measures for each pharmacological condition are given in Fig. 1. The Adjective Mood Scale reflects an impairment of subjective mood by an alteration of its score. Before application of the respective substances the initial scores of the Adjective Mood Scale (Bf-S; Fig. 1A) remained within the normal range of a representative sample of volunteers (46). Three hours after administration of cannabidiol alone, the Adjective Mood Scale reached a mean score of 20.3 ± 12.2 (mean value ± standard deviation) and was significantly altered compared to the initial score ($p = 0.0173$, Wilcoxon test). After administration of nabilone plus placebo, and nabilone plus cannabidiol, the subjective mood was also significantly altered compared to the initial value (17.2 ± 6.8 and 19.1 ± 9.7, respectively; $p = 0.0077$ in both cases). There were no significant differences between the effects of the different pharmacological treatments on subjective mood, thus indicating a general but only medium effect of the different pharmacological manipulations on subjective mood in our experimental setting.

Neither the State-Trait-Anxiety-Inventory (STAI X1) as shown in Fig. 1B nor the Self-Rating Anxiety-Scale (SAS, not shown) revealed significant effects of cannabidiol, nabilone, or their combination on anxiety in our study.

The Bett's Questionnaire upon Mental Imagery (QMI) revealed significant disturbances of the vividness of mental imagery under both conditions in which cannnabidiol was administered (Fig. 1C). With cannabidiol alone, the initial score of 81.8 ± 19.0 was altered significantly to 108.9 ± 51.8 ($p = 0.0117$), while the combined administration of cannabidiol and nabilone significantly increased the score from 82.9 ± 20.3 to 107.2 ± 35.6 ($p = 0.0382$), indicating a less vivid experience of individual mental imagery. Interestingly, with nabilone alone, no marked alteration of this score was detectable.

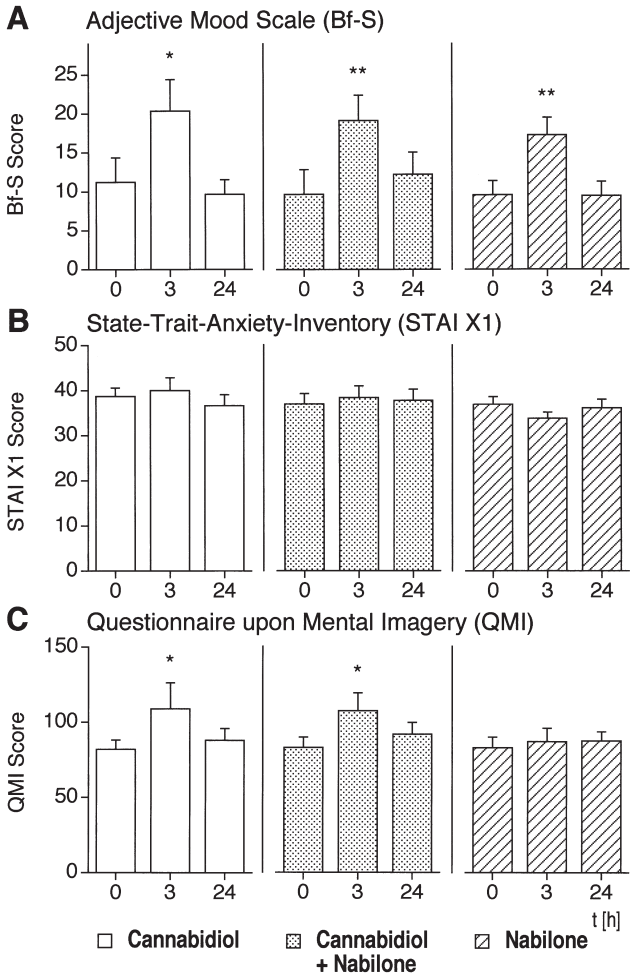

FIG. 1. Behavioural measures before and after oral administration of cannabidiol (200 mg; open bars), cannabidiol (200 mg), and nabilone (1 mg; dotted bars), and nabilone (1 mg; lined bars). Mean values (±standard error of the mean, $n = 9$) of the Adjective Mood Scale are illustrated in A before, 3 and 24 h after administration of the respective substances. (B) Shows mean values (±standard error of the mean, $n = 9$) of the State-Trait-Anxiety-Inventory before, 3 and 24 h after administration of the respective substances. The mean values (±standard error of the mean, $n = 9$) of the respective measures of the questionnaire upon mental imagery are given in C. A Friedman two-way ANOVA was performed for each behavioural measure and each pharmacological intervention. Asterisks indicate the error probability revealed by respective Wilcoxon tests comparing the subsequent values with the initial value where applicable due to the ANOVA (*$p \leq 0.05$; **$p \leq 0.01$).

Binocular Depth Inversion

The depth inversion scores for each class of natural objects and each pharmacological condition are illustrated in Fig. 2. A lower score indicates a more pronounced depth inversion. Initial scores on each experimental day showed no alteration over the course of our experiments. Thus, no learning effect was detectable. Interestingly, the average initial scores for flowers, other ordinary objects, and faces showed no significant paired differences.

After application of cannabidiol alone (Fig. 2, blank bars) no significant alteration was found for binocular depth inversion in all classes of objects investigated. In contrast, binocular depth inversion was significantly impaired after application of nabilone alone (Fig. 2, lined bars). For the ordinary objects and faces we found a significant impairment of binocular depth inversion in all measures after administration of nabilone compared to the initial value ($p \leq 0.05$, Wilcoxon test). It was largest 3 h after administration, with a mean binocular depth inversion score of 0.54 ± 0.14, starting from an initial score of 0.36 ± 0.11 for the ordinary objects and a respective score of 0.50 ± 0.08 increasing from an initial score of 0.32 ± 0.10. With respect to the pharmacokinetics of nabilone, which shows a blood plasma peak about 2 h after oral administration (34), the effects were clearly dose dependent.

The combined administration of cannabidiol and nabilone revealed an interesting pattern of effects on binocular depth

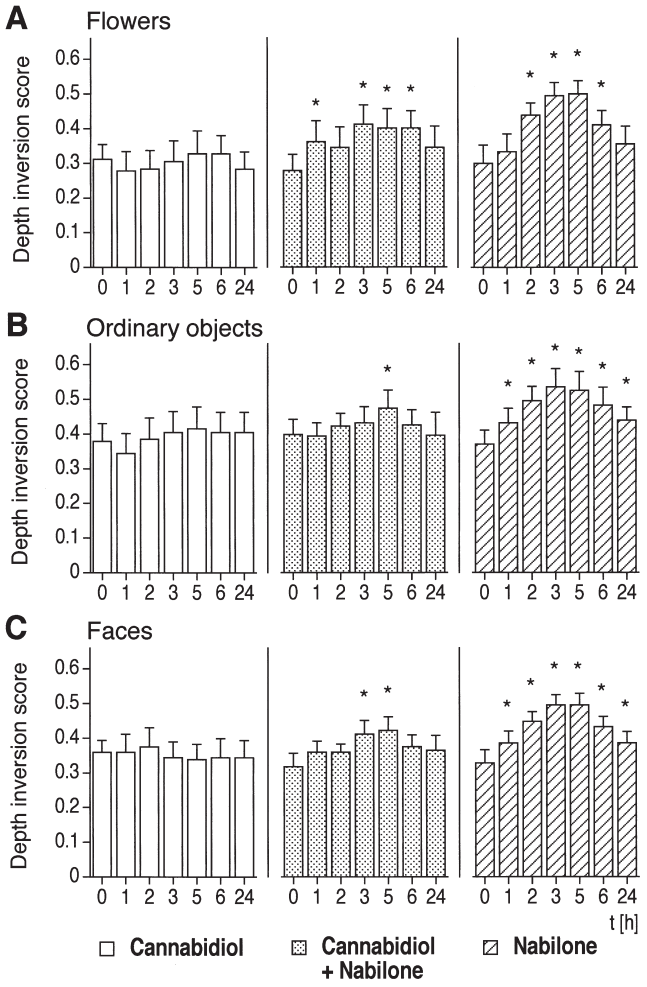

FIG. 2. Depth inversion scores for different classes of objects presented. The mean values of the inversion scores (±standard error of the mean, $n = 9$) are given before and at various time points after the oral administration of cannabidiol (200 mg; open bars), cannabidiol (200 mg) and nabilone (1 mg; dotted bars), and nabilone (1 mg; lined bars). They are shown for the following classes of objects presented: flowers (A), ordinary objects (B), and faces (C). For each class of objects the initial inversion score before drug application (0 h) as well as subsequent inversion scores after oral administration of the respective drugs (1,2,3,5,6, and 24 h) are illustrated. A Friedman two-way ANOVA was performed for each group of objects and each pharmacological intervention. Asterisks indicate the error probability revealed by respective Wilcoxon tests comparing the subsequent values with the initial value where applicable due to the ANOVA ($*p \leq 0.05$).

inversion (Fig. 2, dotted bars). In general, there was an impairment of binocular depth inversion when compared to the administration of cannabidiol alone. Nonetheless, this impairment did not reach the level of that induced by nabilone when given alone. While there were significant alterations of binocular depth inversion of flowers on several occasions after administration of cannabidiol and nabilone (Fig. 2A), the score for the ordinary objects was only significantly altered 5 h after administration of the substances compared to the initial value (Fig. 2B). This was similar for the presentation of faces. where a significant alteration was found 3 and 5 h after administration of both cannabinoids (Fig. 2C).

Comparing the different pharmacological interventions in our series of experiments, we found significant differences between the respective binocular depth inversion scores on several occasions following administration of the substances. These are shown in Table 1. There were no significant differences in the effects of the different cannabinoids 1 and 24 h after administration. While effects on the depth inversion of flowers were significantly altered during the first part of the respective experiments, similar effects were seen in the second part of the experimental day for the ordinary objects. In both cases there was not only a significant difference between the conditions in which both cannabidiol and nabilone were administered alone, but also between the cannabidiol and cannabidiol plus nabilone condition at specified times after administration (see Table 1). By contrast, the values for the recognition of faces were significantly different between the cannabidiol and nabilone conditions 3 and 5 h after administration. Furthermore, there was a significant difference between the cannabidiol plus nabilone and the nabilone alone condition in the early and the late phase after administration, thus indicating a significant reduction of the nabilone-induced impairment of binocular depth inversion by cannabidiol in these cases.

DISCUSSION

The individual and interactive actions of cannabidiol and nabilone on subjective effects and other behavioural measures found in our study correspond well with previous findings in this field (3,19,22,49). Our findings concerning the subjective mood of the volunteers are in line with previous observations where an influence of cannabidiol on subjective experience has been reported (49). However, the Adjective Mood Scale mainly reflects influences on the general well-being, and does not further differentiate the qualities of subjective experience. With respect to the relatively low dosage of nabilone administered, the subjective effects are in line with previous observations that drowsiness and a moderate "high" are common effects of nabilone in clinical use (41).

The absence of an effect of both cannabinoids on anxiety confirms previous findings in healthy volunteers (28,49), even with the much higher dosage of cannabidiol administered in our study. Interestingly, the combined application of both cannabinoids did not reveal any kind of combined effects on anxiety that might have been expected. Although there are some strong conceptual and methodological criticisms directed at the Questionnaire upon Mental Imagery [for review, see (44) and (33)], it is interesting to note that the vividness of mental imagery seems to be reduced under the influence of cannabidiol. On the other hand, we have not seen any effect of nabilone thereon, although it has been reported that marijuana may facilitate imagery (27).

In summary, there is evidence from the behavioural data that the clinical effects are comparable to previously reported conditions. Therefore, our experimental setting provides a valid basis for further analysis of the data on binocular depth inversion.

The data presented here contribute to the question of whether the effects of cannabinoids on binocular depth inversion that have been shown for cannabis resin (8) and synthetic Δ^9-THC (25) are limited to psychotropic cannabinoids. The data shows that this is indeed the case, because binocular depth inversion is not significantly affected by the nonpsychotropic cannabidiol but by the psychotropic nabilone. The time course of the impairment of binocular depth inversion due to

TABLE 1

STATISTIC COMPARISONS BETWEEN BINOCULAR DEPTH INVERSION SCORES AFTER ORAL ADMINISTRATION OF CANNABIDIOL, NABILONE, AND COMBINED ADMINISTRATION OF BOTH SUBSTANCES WITH RESPECT TO THE OBJECT CATEGORIES AND TIME AFTER ADMINISTRATION OF THE RESPECTIVE SUBSTANCES

	2 hours	3 hours	5 hours	6 hours
Flowers				
Cannabidiol vs. nabilone	0.0180	0.0431	n.s.	n.s.
Cannabidiol vs. cannabidiol + nabilone	n.s.	0.0180	n.s.	n.s.
Cannabidol + nabilone vs. nabilone	n.s.	n.s.	n.s.	n.s.
Natural objects				
Cannabidiol vs. nabilone	n.s.	n.s.	0.0425	n.s.
Cannabidiol vs. cannabidiol + nabilone	n.s.	n.s.	0.0330	n.s.
Cannabidol + nabilone vs. nabilone	n.s.	n.s.	n.s.	n.s.
Faces				
Cannabidiol vs. nabilone	n.s.	0.0117	0.0117	n.s.
Cannabidiol vs. cannabidiol + nabilone	n.s.	n.s.	n.s.	n.s.
Cannabidiol + nabilone vs. nabilone	0.0209	n.s.	n.s.	0.0440

p-Values for post hoc paired Wilcoxon tests are given where statistically relevant and applicable after Friedman two-way ANOVA. (n.s.: no significant difference).

nabilone is similar to the reported one for other psychotropic cannabinoids, and appears to be dose dependent with respect to the pharmacokinetics of nabilone (34). Concerning the relative potencies of cannabinoids in humans, the reported effects of synthetic Δ^9-THC (up to 15 mg, oral administration) on binocular depth inversion (25), which have been more pronounced, are comparable to the effects of nabilone (1 mg, oral administration) reported here. This is because nabilone has been found to be five times more effective in humans than Δ^9-THC (15). The data confirms our previous observations that binocular depth inversion shows a sensitive response to psychotropic cannabinoids already at very low doses. Furthermore, our hypothesis that the central nervous endogenous cannabinoid system is involved in perceptual processes on a higher level of information processing is strengthened (25).

Although the underlying mechanisms of binocular depth inversion have been recently revealed in more detail (13,16,45), the basic neural mechanisms of binocular depth inversion still remain an object of further research. So far, there is no indication for an underlying general disturbance of binocular depth perception (45). Regularly, ordinary objects with a higher degree of everyday familiarity (i.e., faces, chairs, or a house), tend to evoke a more pronounced binocular depth inversion (17,40,45). Although similarity of the initial depth inversion scores for the ordinary objects and faces is in line with our previous findings (25,35,36), the initial score for flowers in this study remains somewhat low compared to our previously reported results (25). Nonetheless, we have seen a larger variability of the individual binocular depth inversion of these stimuli when compared to the ordinary objects and faces. Therefore, the latter seem to be more valid stimuli to gain a more differentiated view of impaired binocular depth inversion associated with behavioural or psychiatric disturbances.

As already touched on in the introduction, appealing models and hypotheses regarding the mechanisms involved in binocular depth inversion have been proposed. Gray and Rawlins (12) suggested a comparator system that gauges incoming sensory data (bottom-up) against conceptual knowledge (top-down) This comparator determines the ultimate conscious experience of the outer world. Gray and Rawlins suggested hippocampal structures as a possible site of the comparator mechanism. It has been proposed that internal correcting and adaptive systems may be deficient in psychotic states, and that an imbalance in systems responsible for concept formation occurs (10,26). The issue of whether other structures of the temporal lobes and/or prefrontal cortical areas are involved in these processes is controversial (1,14). Nonetheless, the top-down processing in a sense of correcting (13) is apparently weakened under the influence of psychotropic cannabinoids, resulting in an increase in veridicality for the depth recognition of the ordinary objects and faces.

Interestingly, the combined application of cannabidiol and nabilone revealed some kind of intermediate impairment of binocular depth inversion. Although this impairment is statistically significant compared to the initial value at some time after administration of the substances in all groups of stimuli, it fell far short of the effect of nabilone alone. For the ordinary objects and faces, the early and late phase of the nabilone effects on binocular depth inversion are affected, which is statistically significant for the recognition of faces. These findings correspond well with previous findings that cannabidiol is able to diminish some effects of Δ^9-THC effectively (3,22). Although this has not been found to be the case in general (19), it seems to be the case in our paradigm.

Concerning our model of impaired binocular depth inversion in productive psychotic syndromes (6,36), it may be speculated that these findings are attributable to an antipsychotic action of cannabidiol as it has been reported in animal models (48) and in humans (47). With respect to the latter report, the partial antagonistic action of cannabidiol in this model paradigm might be due to the relatively small dosage of cannabidiol in our experiments compared to the dosage of 1,500 mg/day given under clinical conditions or to a specific action of cannabidiol itself (30). Unfortunately, pharmacokinetic data on a possible interaction of orally administered cannabidiol and nabilone is lacking. Therefore, it remains somewhat speculative to put the interactive effects down to pharmacodynamic interactions of both substances only. Nevertheless, there is no final proof for a pharmacokinetic interaction between at least cannabidiol and Δ^9-THC (21).

Recently, it has been shown that cannabidiol exerts a partial antagonistic activity on the cannabinoid CB_1 receptor as well (30). Furthermore, there is evidence from animal models that other more potent antagonists on the recently described

cannabinoid CB_1 receptor (4) like SR141716 show clinical properties that are similar to the one of atypical neuroleptics in these models (31).

In conclusion, the data presented here strengthen our previous findings on the effects of cannabis resin and Δ^9-THC on binocular depth inversion (6,7,25). The hypothesis that these effects are limited to psychotropic cannabinoids was confirmed. Furthermore, a weak partial antagonistic effect of cannabidiol on the impairment of binocular depth inversion due to nabilone has been shown, that is in line with previous findings in this field (3,22), and may be explained by recent findings on the actions of cannabinoid CB_1 receptor antagonists in animal models predictive of antipsychotic activity (31,48).

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