Pharmacology Biochemistry and Behavior, Vol. 56, No. 4, pp. 803–807, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00426-1

Towards a Cannabinoid Hypothesis of Schizophrenia: Cognitive Impairments Due to Dysregulation of the Endogenous Cannabinoid System

HINDERK M. EMRICH,[1] F. MARKUS LEWEKE[2] AND UDO SCHNEIDER

Department of Clinical Psychiatry, Medizinische Hochschule Hannover, D-30625 Hannover, Germany

Received 2 August 1996; Revised 14 October 1996; Accepted 14 October 1996

EMRICH, H. M., F. M. LEWEKE AND U. SCHNEIDER. *Towards a cannabinoid hypothesis of schizophrenia: Cognitive impairments due to dysregulation of the endogenous cannabinoid system.* PHARMACOL BIOCHEM BEHAV **56**(4) 803–807, 1997.—Cognitive impairments during psychotic episodes are assumed to be caused not only by one single putative classical neurotransmitter dysfunction but also by an impaired equilibrium of the interaction between different neurobiological generators of cognitive processes. Herein, the perceptual abnormalities induced by psychotogenic agents play a major role as tools for the understanding of model psychoses. The recently discovered cannabinoid receptor system with its endogenous ligand anandamide can be regarded as an extremely relevant regulator system, a dysfunctionality of which may explain at least one subtype of endogenous psychoses. Neuropsychological results (three-dimensional inversion illusion) in Δ^9-tetrahydrocannabinol-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schizophrenic psychoses, regarding disturbances in internal regulation of perceptual processes. The relevance of this finding to a general cognitive dysfunction concept of schizophrenic psychosis is discussed. © 1997 Elsevier Science Inc.

Δ^9-THC Endogenous cannabinoid system Psychosis Schizophrenia Human Binocular depth inversion Perceptual disturbance

ACCORDING to the current view, schizophrenia pathogenetically cannot be attributed to only a single causative factor, but rather arises from a complex pattern of pathogenetic conditions. Psychiatric genetics demonstrates the existence of genetic conditions, but nonetheless the inheritance of schizophrenia does not fit simple Mendelian models (3).

Additionally, gender differences, neurostructural abnormalities, and psychosocial deficiencies have also been proposed to play an important part in the etiology of schizophrenic psychoses. The search for neurochemical correlates of schizophrenia has shifted in recent years from the classical dopamine hypothesis to an increased set of various neurotransmitter imbalance models involving not only the dopaminergic system but also glutamatergic, serotonergic, cholinergic, GABAergic, and peptidergic transmission (31). With increased sophistication of biological investigation and pharmacological treatment, it becomes more important to differentiate between subcategories of schizophrenia that may require special therapeutic regimens.

Cannabis sativa is one of the oldest and most widely used drugs in cultural history. Δ^9-Tetrahydrocannabinol (Δ^9-THC) has been identified as the major psychoactive constituent of *Cannabis sativa* (8). Δ^9-THC and agonistic synthetic cannabinoids produce characteristic behavioral, cognitive, and motor effects.

The subjective effects of cannabinoids in humans vary to some extent and are mainly dose related. Following mild cannabis intoxication, drowsiness, euphoria, heightened sensory

[1]Requests for reprints should be addressed to: Hinderk M. Emrich, Department of Clinical Psychiatry—OE7110, Medizinische Hochschule Hannover, D-30623 Hannover, Germany.
[2]Present address: Department of Epileptology, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.

awareness, and altered time perception are reported. Symptoms of moderate intoxication include memory impairment, depersonalization, and mood alteration. Severe intoxications are characterized by decreased motor coordination, lethargy, slurred speech, and postural hypotension. Among the most frequent adverse reactions of cannabis use are acute panic reactions and acute paranoid psychosis. Meanwhile, clinical signs of chronic cannabis consumption may also resemble negative symptoms of schizophrenic disorders (18). The existence of a specific cannabis-induced psychosis, postulated in the 1970s and early 1980s (11,26), is still not established. The fact that users of cannabis have higher levels of different types of psychopathology does not prove a causal relationship (30).

Chopra et al. (2) reported psychotic reactions following the use of cannabis in a group of East Indian marihuana users. Those who had "schizoid" features became overtly schizophrenic during the period of intoxication. In 1976, the paranoid psychosis associated with long-term cannabis use was compared with paranoid schizophrenia in 25 psychiatric patients by Thacore and Shukla (29). In these cases, the cannabis psychosis was characterized by more bizarre behavior, more violence, and panic. Peralta and Cuesta (20) and Rottanburgh et al. (21) found no differences in psychotic symptoms in comparison with non-cannabis-abusing schizophrenic patients, but a decrease in negative symptoms. Andreasson et al. (32) investigated the association between the level of cannabis intake and the development of schizophrenia during a 15-year follow-up study. The relative risk for schizophrenia among high consumers of cannabis was 6.0 compared with nonusers. In 1983, Täschner compared 219 schizophrenic patients with 50 patients exhibiting cannabis psychoses (28). He found no relevant psychopathological differences between these two groups, and suggested that he had observed the final stage of the same underlying pathological process in both.

The molecular basis of the pharmacological activity of cannabis remained an enigma for several decades, until in 1988 a radiolabelled, potent synthetic derivative of Δ^9-THC was demonstrated to bind to brain membranes in a highly selective and specific manner (5). In rats, monkeys, and humans, the highest density of cannabinoid receptors characterized this way is observed in the basal ganglia (globus pallidus, substantia nigra pars reticulata), the molecular layer of the dentate gyrus of the hippocampus, and the cerebellar molecular layer. Receptors are also dense in the neostriatum, the remainder of the hippocampal formation, and the cerebral cortex. Only a little binding is observed in the spinal cord and the brain stem (14,15).

The existence of a central cannabinoid receptor suggested the presence of endogenous cannabimimetic ligands. In 1992, the first endogenous ligand was discovered (6). Anandamide, an ethanolamide of arachidonic acid, behaves as a typical cannabimimetic compound in several in vitro and in vivo tests. At present, there are three anandamide type mediators, but the physiological role of the anandamide/cannabinoid system remains unknown still (12).

The high receptor levels of the cannabinoid system in limbic system strongly suggest that the cannabinoid/anandamide system may be involved in higher cognitive and emotional functions. Furthermore, the receptor distribution in the basal ganglia and cerebellum points to a role of this endogenous system in motor control as well.

Interestingly, neurological disturbances have been found to a moderate extent in patients with acute schizophrenic psychoses (13,24). These neurological soft signs are not related to any drug-induced dyskinetic disturbances (13,17).

Due to the fact that the endogenous cannabinoid system has been discovered only recently, there is only limited knowledge on its physiological role. On the other hand, through previous research, promising biological markers for schizophrenia have been identified. Abnormalities in eye movement, electrodermal activity, event-related brain potentials, attention and informational processing, and brain imaging have been reported. Studies of potential trait markers suffer from the lack of a standardized methodology, which makes comparisons of their results difficult. Because of the heterogeneity of the disease, it does not come as a surprise to us that no one possible marker appears specific for schizophrenia (27).

Nevertheless, patterns of neuropsychological disturbances may point to specific cognitive disturbances associated with subgroups of schizophrenia. Therefore, it has become part of our approach to psychotic disturbances to investigate visual illusionary perception under various conditions. The investigation of visual illusions has already been established in schizophrenic patients, as well as in various psychiatric syndromes (7,23). Binocular depth inversion represents an illusion of visual perception. Under certain conditions, stereoscopically presented objects with concave depth information are perceived by the observer as convex. Such an illusionary inversion of visual perception does not occur in all cases, but does occur especially when objects with a higher degree of contextual relevance (e.g., photographs of faces) are displayed. In these cases, the plausibility control mechanisms of the perceptual processes are assumed to override the binocular disparity cues of stereopsis. This causes a correction of implausible perceptual hypotheses.

We used this already established model of perceptual disturbance to search for further similarities between cannabis-induced psychedelic states and psychotic conditions.

METHODS

Seven healthy male volunteers (aged 26–42 years) intoxicated with cannabis resin, 13 schizophrenic patients (aged 21–52 years, 8 females and 5 males), and 20 healthy volunteers (control group; aged 20–48 years, 13 females and 7 males) participated in the study. The control group was recruited from hospital medical staff or related volunteers. The volunteers were asked about intake of psychopharmacological medication and their history of psychiatric problems, and were excluded from the study if there was a positive response. The patients had received a diagnosis of schizophrenia according to DSM IV and ICD 10 criteria. Mean scores on the Brief Psychiatric Rating Scale (BPRS) were 39. The schizophrenic patients had been consecutively admitted to the psychiatric unit at the Medical School, Hannover. All had vivid productive symptoms (auditory hallucinations and acute delusions, e.g., depersonalization and derealisation experience, etc.). Additionally, the Positive and Negative Symptoms Scale (PANSS) was used.

Before starting the investigation, stereopsis of the participants was tested using the TNO test for stereoscopic vision (Lameris, Utrecht) and had to amount to at least 60 seconds of arc in each object. Different stereoscopically taken slides were displayed in random order by a device with two slide projectors using cross-oriented linearly polarized light and glasses with corresponding filters for the patients and the healthy volunteers. Pseudoscopy was induced by exchanging the slides in the projectors from right to left and vice versa, as more briefly described elsewhere (23). Every slide set was displayed for 30 s. As a control paradigm to exclude response

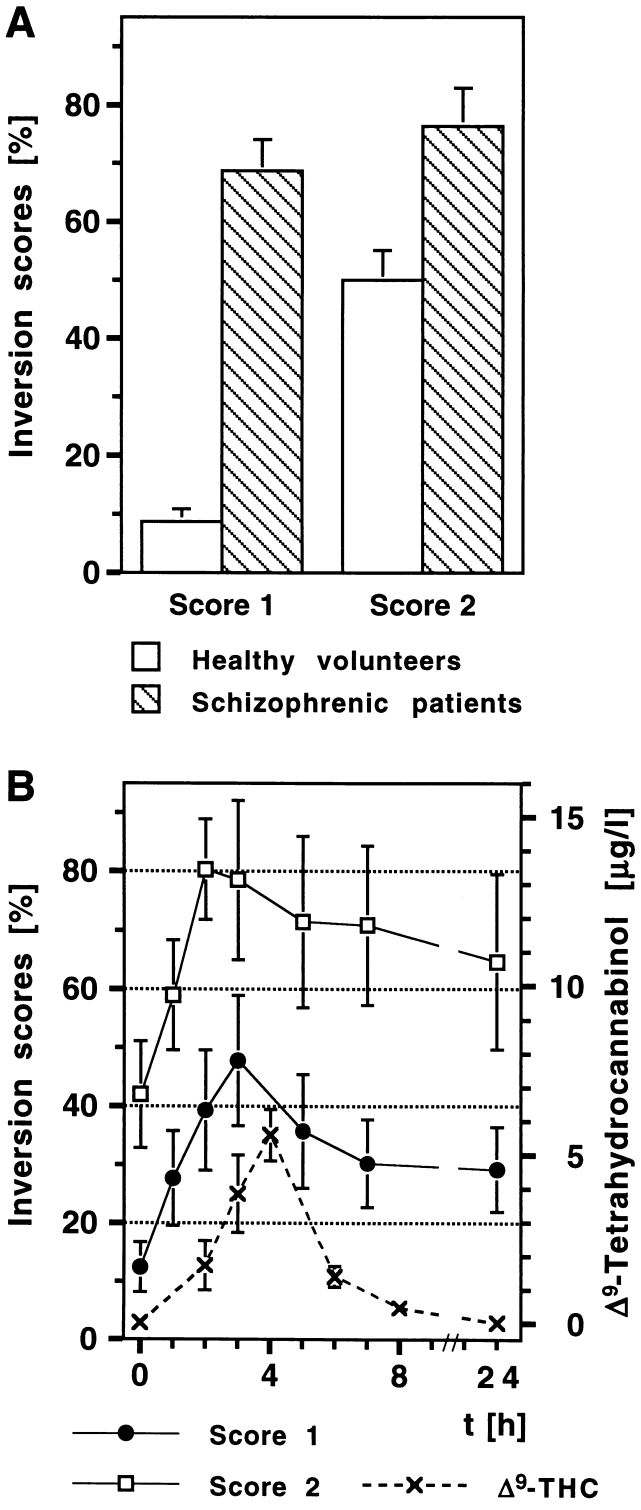

FIG. 1. (A) Inversion scores in schizophrenic patients (mean ± SEM, $n = 13$) and healthy control subjects ($n = 20$) after presentation of objects with a higher degree of familiarity and contextual relevance in daily life (score 1) and with a lower degree of these characteristics (score 2). (B) Time course of inversion scores as in A ($n = 7$) before and at several points after oral intake of a defined dosage of cannabis resin. Filled dots represent values of score 1; open squares indicate values of score 2. The average plasma level of Δ^9-tetrahydrocannabinol is indicated by cross symbols and belongs to the ordinate on the right ($n = 7$).

bias effects, slide sets were displayed either reversed from left to right or not reversed in random order. Only slides with different natural images were used (e.g., faces, houses, flowers). All subjects underwent a physical examination before starting the investigation and gave their informed consent prior to their inclusion in the study. All volunteers included in the cannabis experiment were trained physicians who were informed about possible actions of cannabinoids and participated in the sense of a self-experiment according to the Declaration of Helsinki.

Patients and volunteers described their visual experience during pseudoscopic projection by the following procedure. Score 1 is constituted from the data from slides of objects exhibiting a high degree of familiarity and contextual relevance in daily life (e.g., human face, house, chair, teddy mask). A description of three criteria within every slide was given that characterized binocular depth perception of special parts of the object (i.e., description of depth perception of, e.g., nose, eyes, cheeks, roof, etc.). A maximal score of two points was reached on every slide if the three criteria were fulfilled within 30 s. A similar procedure was used to constitute score 2 (i.e., brushwood, flowers), in which objects contextually less relevant in daily life and with a lower degree of familiarity were visualized. In score 1, a maximum of 8 points (= 100%) and in score 2 a maximum of 4 points (= 100%) could be attained.

After initial determination of the initial scores, the seven healthy volunteers took about 300 mg of cannabis resin (222–373 mg) and after 1, 2, 3, 5, 7, 24, and 192 h the inversion score was measured. Additionally, plasma levels of Δ^9-THC were measured every hour.

For statistical analysis between the schizophrenic patients and the control groups the Mann–Whitney *U*-test and between the inversion scores of the volunteers before and after intake of cannabis resin the Wilcoxon test was applied. Differences were considered significant if the probability of error was $p < 0.05$. Data were analyzed using SPSS (Statistical Package for the Social Sciences) Version 6.1 for the Apple Macintosh.

The standardized cannabis resin used in these experiments was provided by the Institute of Forensic Medicine of the University of Munich.

RESULTS

The results for the schizophrenic patients are shown in Fig. 1A. Score 1 (pictures with a high degree of familiarity) was highly elevated in patients with productive psychotic symptoms [68.7 ± 5.43% (mean ± SEM), $n = 13$] in comparison with the healthy volunteers (8.7 ± 2.18%, $n = 20$). The difference is statistically highly significant ($p < 0.001$, Mann–Whitney test, two-tailed). In score 2 (pictures with a lower degree of familiarity), the results are analogous, but the differences are less pronounced ($p < 0.05$). When visual information was displayed to the correct eye, there were no significant differences between the scores of the patients and the controls.

The time course of the inversion scores of the volunteers after intake of cannabis resin is illustrated in Fig. 1B. Score 1 for presented objects exhibiting a high degree of familiarity and contextual relevance in daily life was significantly elevated from a baseline of 12.5 ± 4.31% ($n = 7$) to a maximum of

47.77 ± 11.14% ($n = 7$, $p < 0.02$, Wilcoxon test, two-tailed) 3 h after cannabis intake. Score 2 for objects with a lower degree of familiarity and contextual relevance in daily life was also significantly elevated. The initial score 2 started with a significantly higher value than score 1 ($p < 0.05$, Wilcoxon test, two-tailed), which has been related to the previously mentioned degree of contextual relevance in daily life (23). Again, the maximum was reached after 2–3 h ($p < 0.03$, Wilcoxon test, two-tailed). This correlates very well with plasma levels of Δ^9-THC (Fig. 1B).

There was a moderate recovery of the initial scores 24 h after cannabis intake. The difference between the initial and the postintoxication score may be attributed to a kind of learning effect. This possible learning effect will be the subject of further investigation.

DISCUSSION

In the context of various clinical reports of the last decades that have noted cannabis-induced schizophrenia-like psychotic states, the reduced internal censorship processes in schizophrenic patients as well as in cannabis- or Δ^9-THC-intoxicated healthy volunteers yield further evidence regarding a role of the endogenous cannabinoid/anandamide system in schizophrenic psychoses.

There is still a lag between the current knowledge of the basic mechanisms of endogenous cannabinoid function, but there are three especially interesting findings with regard to other neurobiological mechanisms possibly involved in the etiology of psychoses.

First, there is the possible direct role of cannabinoid function in the process of psychotic experience that is suggested to be mimicked by the intake of psychedelic cannabinoid receptor ligands such as Δ^9-THC. Our results point to some extent to similar disturbances of perceptual processes in schizophrenic patients and cannabis-intoxicated healthy volunteers. Whether these disturbances underlie other symptoms occurring in psychoses remains to be investigated.

Second, Gardner et al. studied the pharmacological relation between the psychotic symptoms of schizophrenic patients and cannabis abuse (9,10). They found that Δ^9-THC acts as a dopamine agonist in dopaminergic projections of the medial forebrain bundles. Also, there are further reports of dopaminergic interactions of cannabinoids, though the mechanism of interaction still remains unclear (22). The dopamine hypothesis of schizophrenia postulates that increased brain dopaminergic activity causes psychotic symptoms of schizophrenia (4). This hypothesis is supported by the capacity of dopaminergic drugs to cause paranoid psychoses and pharmacological studies showing that antipsychotic drugs antagonize postsynaptic D_2-receptors (25). In many studies, the intensity of cannabis abuse was correlated with an increase of psychotic relapses. According to this model, an increased Δ^9-THC level, acting as a dopamine agonist, leads to an increased dopaminergic tone in the projections of the medial forebrain.

Third, Mailleux and Vanderhaeghen reported on the upregulation of cannabinoid receptor gene expression in the rat caudate putamen by glutamate through the *N*-methyl-D-aspartate (NMDA) receptor subtype (19). These findings indicate a tight link of the endogenous cannabinoid system not only to the dopaminergic system but also to the glutamatergic system, and may point to another interactional linkage between these receptor systems already discussed in relation to psychotic conditions (1).

Neurological soft signs, especially motor deficiencies, were described before the neuroleptical treatment started in the 1940s, and they frequently occur in the clinical course of endogenous psychoses. Autoradiographic localization of brain cannabinoid receptors has revealed a unique distribution, with the greatest density in the basal ganglia, the hippocampus, and the cerebellum. The basal ganglia and the cerebellum are regions that coordinate motor functions. In humans, impaired coordination and balance, decreased muscle tone, and tremor are frequently observed after cannabis intake (16). This strongly suggests that the cannabinoid/anandamide system is involved in this activity, and an impairment of this system could also explain the neurological soft signs during endogenous psychosis.

In our concept, cannabis abuse is at least not merely a stressor for psychotic relapse and exacerbation of schizophrenic syndromes. Moreover, a subgroup of schizophrenic syndromes may pathogenetically be related to a functional disturbance of the endogenous cannabinoid/anandamide system. At present, this hypothesis needs to be evaluated further by studies on the basic mechanisms of the endogenous cannabinoid system and integration of new investigational tools like selective cannabinoid receptor antagonists into clinical studies. From our point of view, it may lead to some new approaches in the treatment of schizophrenic psychoses.

REFERENCES

1. Bowers, M. B., Jr.; Morton, J. B.: Regional brain catecholamines and metabolites following THC, PCP and MK-801. Prog. Neuropsychopharmacol. Biol. Psychiatry 18:961–964; 1994.
2. Chopra, G. S.; Smith, J. W.: Psychotic reactions following cannabis use in East Indians. Arch. Gen. Psychiatry 30:24–27; 1974.
3. Ciaranello, R. D.; Ciaranello, A. L.: Genetics of major psychiatric disorders. Annu. Rev. Med. 42:151–158; 1991.
4. Crow, T. J. Molecular pathology of schizophrenia: More than one disease process? Br. Med. J. 280:66–68; 1980.
5. Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C.: Determination and characterization of a cannabinoid receptor in rat brain. Mol. Pharmacol. 34:605–613; 1988.
6. Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R.: Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946–1949; 1992.
7. Emrich, H. M.: A three-component-system hypothesis of psychosis. Impairment of binocular depth inversion as an indicator of a functional dysequilibrium. Br. J. Psychiatry 155:S37–S39; 1989.
8. Gaoni, Y.; Mechoulam, R.: Isolation, structure and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86:1646–1647; 1964.
9. Gardner, E. L.; Lowinson, J. H.: Marijuana's interaction with brain reward systems: Update 1991. Pharmacol. Biochem. Behav. 40:571–580; 1991.
10. Gardner, E. L.; Paredes, W.; Smith, D.; Donner, A.; Milling, C.; Cohen, D.; Morrison, D.: Facilitation of brain stimulation reward by delta 9-tetrahydrocannabinol. Psychopharmacology (Berl.) 96:142–144; 1988.
11. Halikas, J. A.; Goodwin, D. W.; Guze, S. B.: Marijuana use and psychiatric illness. Arch. Gen. Psychiatry 27:162–165; 1972.
12. Hanus, L.; Gopher, A.; Almog, S.; Mechoulam, R.: Two new

unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor. J. Med. Chem. 36:3032–3034; 1993.
13. Heinrich, D. W.; Buchanan, R. W.: Significance and meaning of neurological signs in schizophrenia. Am. J. Psychiatry 145: 11–18; 1988.
14. Herkenham, M.; Lynn, A. B.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C.: Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. J. Neurosci. 11:563–583; 1991.
15. Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C.: Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci. USA 87:1932–1936; 1990.
16. Hollister, L. E.: Health aspects of cannabis. Pharmacol. Rev. 38:1–20; 1986.
17. King, D. J.; Wilson, A.; Cooper, S. J.; Waddington, J. L.: The clinical correlates of neurological soft signs in chronic schizophrenia. Br. J. Psychiatry 158:770–775; 1991.
18. Kupfer, D. J.; Detre, T.; Koral, J.; Fajans, P.: A comment on the "amotivational syndrome" in marijuana smokers. Am. J. Psychiatry 130:1319–1321; 1973.
19. Mailleux, P.; Vanderhaeghen, J. J.: Glutamatergic regulation of cannabinoid receptor gene expression in the caudate-putamen. Eur. J. Pharmacol. 266:193–196; 1994.
20. Peralta, V.; Cuesta, M. J.: Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr. Scand. 85:127–130; 1992.
21. Rottanburgh, D.; Robins, A. H.; Ben-Arie, O.; Teggin, A.; Elk, R.: Cannabis-associated psychosis with hypomanic features. Lancet 2:1364–1366; 1982.
22. Sakurai-Yamashita, Y.; Kataoka, Y.; Fujiwara, M.; Mine, K.; Ueki, S.: Δ^9-Tetrahydrocannabinol facilitates striatal dopaminergic transmission. Pharmacol. Biochem. Behav. 33:397–400; 1989.
23. Schneider, U.; Leweke, F. M.; Sternemann, U.; Weber, M. M.; Emrich, H. M.: Visual 3D illusion: A systems-theoretical approach to psychosis. Eur. Arch. Psychiatry Clin. Neurosci. 246:256–260; 1996.
24. Schröder, J.; Richter, P.; Geider, F. J.; Niethammer, R.; Binkert, M.; Reitz, C.; Sauer, H.: Diskrete motorische und sensorische Störungen (neurologische soft signs) im Akutverlauf endogener Psychosen. Z. Klin. Psychol. Psychopathol. Psychother. 41:190–206; 1993.
25. Seeman, P.; Van Tol, H. H.: Dopamine receptor pharmacology. Trends Pharmacol. Sci. 15:264–270; 1994.
26. Spencer, D. J.: Cannabis induced psychosis. Br. J. Addict. 65:369–372; 1970.
27. Szymanski, S.; Kane, J. M.; Lieberman, J. A.: A selective review of biological markers in schizophrenia. Schizophr. Bull. 17:99–111; 1991.
28. Täschner, K. L.: Zur Psychopathologie und Differentialdiagnose sogenannter Cannabispsychosen. Fortschr. Neurol. Psychiatr. 51:235–248; 1983.
29. Thacore, V. R.; Shukla, S. R.: Cannabis psychosis and paranoid schizophrenia. Arch. Gen. Psychiatry 33:383–386; 1976.
30. Thomas, H.: Psychiatric symptoms in cannabis users. Br. J. Psychiatry 163:141–149; 1993.
31. Wright, I.; Woodruff, P.: Aetiology of schizophrenia. A review of theories and their clinical and therapeutic implications. CNS Drugs 3:126–144; 1995.
32. Andreasson, S.; Allebeck, P.; Rydberg, U.: Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. Acta Psychiatr. Scand. 79:505–510.