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Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome

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High densities of cannabinoid receptors were found in the basal ganglia and hippocampus, indicating a putative functional role of cannabinoids in movement and behaviour. Anecdotal reports suggested beneficial effects of marijuana in Tourette's syndrome (TS). We therefore interviewed 64 TS patients with regard to use of marijuana and its influence on TS symptomatology. Of 17 patients (27%) who reported prior use of marijuana, 14 subjects (82%) experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and obsessive-compulsive symptoms. Our results provide more evidence that marijuana improves tics and behavioural disorders in TS. It can be speculated that cannabinoids might act through specific receptors, and that the cannabinoid system might play a major role in TS pathology.

Key words: Tourette's syndrome; tic; marijuana; *Cannabis sativa*; cannabinoids

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Introduction

Gilles de la Tourette syndrome (Tourette's syndrome, TS) is a complex neuropsychiatric disorder of unknown aetiology, characterized by waxing and waning motor and vocal tics and a variety of associated behavioural disorders such as obsessive-compulsive symptoms (OCS), lack of impulse control, attention deficit hyperactivity disorder (ADHD), anxiety, depression, and self-injurious behaviour. Several studies have provided evidence that basal ganglia circuits projecting to the frontal cortex and to limbic regions are pathophysiologically involved. Furthermore, the dopaminergic system seems to play an active role in TS pathology, but imbalances of several other neurotransmitter systems have been suggested to be the primary cause of the disease. Dopamine-blocking neuroleptics are the most effective drugs for the treatment of tics. However, other drugs are necessary to control associated behavioural disorders, e.g. serotonin reuptake inhibitors for OCS or methylphenidate for ADHD (1).

Anecdotal reports have suggested beneficial effects of marijuana (*Cannabis sativa*) in TS. Sandyk and Awerbuch (2) reported that three TS patients experienced a significant amelioration of symptoms when using marijuana. These 15- to 39-year-old male patients had noted an improvement of tic severity, urge to tic, self-mutilatory behaviour, attention span, hypersexuality and a generalized relaxation when they smoked half to two marijuana cigarettes per day. Hemming and Yellowlees (3) described a single case of a 36-year-old man who had reported that he had been symptom free for more than 1 year while he was taking one 'cone' of marijuana per night.

The aim of the present study was to investigate further the influence of marijuana smoking in patients suffering from TS. We therefore interviewed a large group of TS patients with regard to subjective experiences of marijuana use, employing a standardized format.

Material and methods

A total of 64 consecutive patients (55 males and 9 females, mean age 30.3 years, range 15–64 years) suffering from TS according to DSM-III-R criteria were interviewed by one of the authors (K.R.

Table 1. Clinical details, frequency, amount and effect of marijuana use in 17 TS patients

Patient no.	Age (years)/sex	STSS	OCS	ADHD	Medication	Kind of use	Effect of marijuana
1	34/M	5	3	+	—	1–2 cigarettes/day, occasionally	Remission of OCS, MT, VT
2	22/M	4	1	+	—	1–2 cigarettes/day, occasionally	Reduction in pre-urges, MT, VT
3	40/M	4	3	+	NL	1–2 cigarettes/week, occasionally	Reduction in MT, VT
4	18/M	3	2	+	—	5–6 cigarettes/week, regularly	Reduction in MT, VT
5	16/M	4	1	+	NL	1–2 cigarettes/week, occasionally	Reduction in MT, VT
6	24/M	2	3	+	—	3–4 cigarettes/day, regularly	Reduction in pre-urges, MT, VT, ADHD
7	38/M	3	3	+	NL, SRI	<1 cigarette/week, occasionally	Reduction in MT, VT
8	31/M	2	3	—	—	1 cigarette twice	Reduction in pre-urges
9	19/M	1	2	—	NL	1 cigarette once	Reduction in MT, VT
10	22/M	2	1	—	NL	1 cigarette/month, occasionally	Remission of MT, VT
11	36/F	5	3	+	NL, SRI	1 cigarette twice	Reduction in MT, VT
12	32/M	2	2	—	—	1 cigarette once	Remission of MT, VT
13	25/M	3	1	—	—	1–2 cigarettes/week, occasionally	Reduction in pre-urges, MT, VT
14	42/F	4	3	+	—	1 cigarette once	Remission of MT, VT
15	39/M	5	3	—	—	2 cigarettes once	No influence
16	37/M	4	3	—	—	1 cigarette/week, occasionally	No influence
17	44/M	3	3	+	NL	1 cigarette twice	No influence

STSS, Shapiro Tourette Syndrome Severity Scale; OCS, obsessive-compulsive symptoms (0=none, 1=mild, 2=moderate, 3=marked); ADHD, attention deficit hyperactivity disorder; NL, neuroleptics; SRI, serotonin reuptake inhibitor; MT, motor tics; VT, vocal tics; pre-urges, premonitory urges.

M.-V.). All patients were recruited from our movement disorder clinic. The diagnosis of TS was independently established by two of the authors (K.R. M.-V. and H.K.). Using a structured interview we questioned all patients about use of marijuana, frequency and duration of use, the amount of drugs used, and the influence on both tics and behavioural disorders. The type of chronic medication administered for TS, comorbid diagnoses of OCS (clinically rated as none, mild, moderate or marked) and ADHD, and tic severity according to the Shapiro Tourette Syndrome Severity Scale (STSS) (range 0–6, where 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = marked, 5 = severe and 6 = very severe) (4) are summarized in Table 1. A physical and neurological examination was conducted to exclude other disorders. None of the patients suffered from a psychotic disorder. Informed written consent was obtained from each individual.

Results

Of 64 interviewed patients, 17 subjects (27%) (15 males and 2 females, mean age 30.5 years, range 16–44 years) reported previous use of marijuana. Of these, 2 patients had regularly smoked for a longer period of time (>1 year) and 15 patients reported occasional use of marijuana. Overall, 14 patients (82%) (12 males and 2 females) experienced a marijuana-induced improvement of their symptoms. Nine patients (nos 2–7, 9, 11 and 13) noted a moderate or marked reduction, and four (nos 1, 10, 12 and 14) reported a complete remission of both motor and vocal tics. Patient no. 8 only experienced improvement of premonitory urges. One of these patients (no. 1) suffered from extreme coprolalia, and reported that this has stopped since he has been smoking marijuana. One patient also noted a remission of OCS, another reported an amelioration of attention deficit, and four noted an improvement of premonitory urges. Three patients (18%) reported no influence on any of their symptoms. No differences in tic severity, associated behavioural disorders and chronic medication could be found between these three patients and those who experienced an improvement. None of the patients reported a deterioration of symptoms when they were smoking marijuana. Beneficial effects were noted both by patients without medication and by those treated with neuroleptics and/or serotonin reuptake inhibitors (Table 1).

Two patients noted beneficial effects when they smoked occasionally and smoked 1–2 marijuana cigarettes per week, respectively, but reported no more effect when they were smoking regularly (no. 10) and using higher amounts (no. 13), respectively. In contrast, patients 4 and 6 had regularly smoked marijuana for more than 3 and 5 years, respectively, and experienced no decrease in efficacy. Patient 6 therefore stopped less effective medical treatment with pimozide. All of the patients who experienced an improvement reported that the beneficial effects lasted for at least from 3–4 h up to 1 day. One patient (no. 11), who had used marijuana only twice, noted an exacerbation of tics the following day. The frequency and duration of use, as well as the doses used, are summarized in Table 1. None of the patients reported any serious side-effects when smoking marijuana.

Discussion

Our results are highly consistent with previous anecdotal reports (2, 3) suggesting an essential improvement in symptoms of TS when smoking marijuana. Of 17 patients who reported use of marijuana, 14 subjects (82%) experienced a marked amelioration of symptoms. While most patients noted a reduction or complete remission of both motor and vocal tics, some also reported an improvement of premonitory urges, OCS and ADHD.

To date, the exact neuroanatomical localization and the underlying pathophysiology of TS are not known. There are numerous theories about the primary cause of the disease. Dysfunction of several central neurotransmitter systems has been suggested, including the dopaminergic, serotoninergic, noradrenergic, cholinergic, gamma-aminobutyric acid (GABA)-ergic and opioid systems. In addition, it has been speculated that imbalances within different transmitter systems or an abnormality involving a second messenger system might underlie TS pathology (1).

However, several studies have provided strong evidence that the dopaminergic system plays an active role in the pathophysiology of TS. Dopamine-blocking drugs reduce tics, dopamine agonists enhance tics, and the level of the dopamine metabolite homovanillic acid has been found to be reduced in the cerebrospinal fluid of TS patients. Furthermore, neuroimaging studies demonstrated increased dopamine transporter binding using ^{123}I-β-CIT-single photon emission computed tomography (SPECT) (5) and different dopamine D_2 receptor binding in monozygotic twins discordant for TS using ^{123}I-IBZM-SPECT (6). Nevertheless, in clinical practice the therapy for tics is often difficult, and associated behavioural disorders remain uninfluenced by neuroleptic treatment. Consequently, it can be speculated that the dopaminergic system is not the primary cause of TS, but that it is secondarily involved.

Due to the present findings of a marked improvement in TS symptomatology when smoking marijuana, we propose a new hypothesis for the neurobiological pathogenesis of the disease, suggesting the involvement of the cannabinoid system. Recently, cannabinoid receptors have been localized with a very high density in the outflow nuclei of the basal ganglia (globus pallidus and substantia nigra pars reticulata), and in the molecular layers of the cerebellum and hippocampal dentate gyrus. Dense binding was also observed in the cerebral cortex, other parts of the hippocampal formation, and the striatum (7). In addition, cannabinoid receptors were found to be co-localized both with dopamine D_1 receptors on striatonigral dynorphin/substance-P-containing neurones and with dopamine D_2 receptors on striatopallidal enkephalinergic neurones (8). It has therefore been suggested that cannabinoids might influence dopaminergic processes and that they might regulate motor activity (7, 8).

Several studies in rats support the hypothesis of an interaction between the cannabinoid and dopamine systems. Moss et al. (9) demonstrated that cannabinoids potentiated neuroleptic-induced hypokinesia, and Rodriguez de Fonseca et al. (10) found that perinatal exposure to cannabinoids altered the normal development of nigrostriatal dopaminergic neurones. Furthermore, it has been shown that acute exposure to delta-9-tetrahydrocannabinol (Δ^9-THC), the most psychoactive ingredient of *Cannabis sativa*, decreases the number of striatal D_2 dopaminergic binding sites (11). Repeated stimulation of dopamine D_1 receptors enhanced catalepsy in male rats induced by the potent cannabinoid receptor agonist (-)-11-hydroxy-Δ^8-tetrahydrocannabinol-dimethylheptyl (12). The cannabinoid agonists WIN 55,212–2 and CP 55,940 were found to attenuate contralateral rotational behaviour induced by a dopamine D_1 agonist in rats with unilateral lesions of the nigrostriatal pathway (13). In addition, it could be demonstrated that anandamide, identified as an endogenous ligand of the cannabinoid receptor (14), reduced locomotor activity (15). In humans, beneficial effects of cannabinoids have been reported in tremor (16) and dystonia (17), whereas in parkinsonism an 'aggravating' effect was observed (18).

We postulate that in TS the beneficial effects of marijuana are due to a specific action on central cannabinoid receptors. Furthermore, due to the reasonable theory of involvement of the dopamine

system in TS pathology, it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine receptors in basal ganglia. Several studies have confirmed that cannabinoids can alter brain dopaminergic neurotransmission and are involved in motor control (7, 11).

In addition, there is much evidence that cannabinoids influence not only movement but also behaviour, cognition and emotional functions. In healthy marijuana users psychic changes with a period of euphoria or a 'high', as well as cognitive impairments such as distractibility, fragmentation of thoughts and difficulty in solving problems and, in addition, anxiety, an acute paranoid state, acute mania and confusion have been described (19). Impairment of attention, visuospatial memory (20) and binocular depth inversion (21) has been observed. Moreover, an association between the endogenous cannabinoid system and schizophrenic psychoses has been suggested (22). It has therefore been postulated that the psychological consequences and cognitive impairments associated with cannabis use might be mediated by cannabinoid receptors located in the cortex and hippocampus (7, 23).

Previous case reports, as well as our results, have provided much evidence that marijuana smoking improves not only tics but also associated behavioural disorders such as OCS, attention deficit, self-injurious behaviour and premonitory urges. It can therefore be postulated that the improvement of associated behavioural disorders might be due to a regulatory modulation of cannabinoid receptors in the cortex and hippocampus.

Naturally, a study based on a retrospective survey of patients' subjective experiences has some limitations. The possibility cannot entirely be excluded that clinical improvement associated with marijuana use was caused by non-specific mechanisms such as reduction of anxiety, sedation, euphoria, or the mere fact of using an illegal drug. However, we suggest that such non-specific mechanisms cannot adequately explain the beneficial effects reported in such a large number of patients. It seems very unlikely that the fact of using an illegal drug was a meaningful explanation, because some of the patients reported use of other illegal drugs, e.g. LSD and cocaine, and noted no influence on or even a deterioration of their symptoms. Another problem is that no examiner rating scales could be used to confirm subjective experiences, because the results were obtained from retrospective patients' reports. In addition, the clinical course of TS is characterized by spontaneous waxing, waning, fluctuation and remission of tics. These natural changes are a well-known shortcoming of interviews, self-reporting scales and even examiner ratings in TS. The fact that an improvement in associated behavioural disorders was noted less commonly than tic improvement should be interpreted with caution. Most patients used marijuana only occasionally, and therefore it has to be assumed that tic improvement was noticed to a much greater extent than beneficial effects on behavioural disorders. Moreover, it has yet to be established why some patients experienced no effect at all, and why some patients noted a decrease in efficacy when they were smoking regularly, while others did not. Another problem with this retrospective study is that patients used different amounts of marijuana, and also very probably used marijuana containing different ingredients. However, this fact might explain why some patients noted greater effects than others. It is still unclear which of the multiple components of marijuana might cause the supposedly beneficial effects. Further studies are needed to address all of these issues.

Therefore, in an uncontrolled open clinical trial we treated one TS patient with Δ^9-THC, the major psychoactive ingredient of marijuana, and observed a marked improvement of tics on a self-reporting scale as well as on examiner rating. These preliminary results suggest that the beneficial effects of marijuana might be due to Δ^9-THC (24).

In conclusion, clinical reports and *in vitro* studies have suggested that cannabinoids might modulate motor activity, alter dopaminergic neurotransmission and influence behaviour. Our results provide substantial evidence that marijuana smoking improves tics and associated behavioural disorders in TS. It can therefore be postulated that the cannabinoid system might play a major role in the pathophysiology of TS. Furthermore, we postulate that marijuana and its ingredients might be an effective treatment for TS.

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