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Cannabis in Movement Disorders

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Key Words

Movement disorders · Tourette syndrome · Tics · Chorea · Huntington's disease · Parkinson's disease · Parkinsonian syndromes · Dystonia · Levodopa-induced dyskinesia · Tremor · Nabilone · Cannabidiol · Δ^9-THC · Glutamate · GABA · Dopamine

Summary

Central cannabinoid receptors are densely located in the output nuclei of the basal ganglia (globus pallidus, substantia nigra pars reticulata), suggesting their involvement in the regulation of motor activity. Furthermore, there is evidence that endogenous cannabinoid transmission plays a role in the manipulation of other transmitter systems within the basal ganglia by increasing GABAergic transmission, inhibiting glutamate release and affecting dopaminergic uptake.

Most hyperkinetic and hypokinetic movement disorders are caused by a dysfunction of basal ganglia-thalamo-cortical loops. It has been suggested that an endogenous cannabinoid tone participates in the control of movements and, therefore, the central cannabinoid system might play a role in the pathophysiology of these diseases.

During the last years in humans a limited number of clinical trials demonstrated that cannabinoids might be useful in the treatment of movement disorders. Despite the lack of controlled studies there is evidence that cannabinoids are of therapeutic value in the treatment of tics in Tourette syndrome, the reduction of levodopa-induced dyskinesia in Parkinson's disease and some forms of tremor and dystonia. It can be speculated that cannabinoid antagonists might be useful in the treatment of chorea in Huntington's disease and hypokinetic parkinsonian syndromes.

Schlüsselwörter

Bewegungsstörungen · Tourette Syndrom · Tics · Chorea · M. Huntington · M. Parkinson · Parkinson-Syndrom · Dystonie · Levodopa-induzierte Dyskinesie · Tremor · Nabilon · Cannabidiol · Δ^9-THC · Glutamat · GABA · Dopamin

Zusammenfassung

Cannabis bei Bewegungsstörungen

Zentrale Cannabinoid-Rezeptoren konnten in besonders hohen Konzentrationen in den Ausgangsstrukturen der Basalganglien (Substantia nigra pars reticulata, Globus pallidus) nachgewiesen werden. Cannabinoide üben vermutlich eine Regulatorfunktion innerhalb der Basalganglien aus, indem sie die GABAerge Hemmung verstärken, die glutamaterge Stimulation reduzieren und das dopaminerge Systems modulieren. Zudem scheint ein endogener Basistonus des Cannabinoidsystems für die Funktion des extrapyramidal-motorischen Systems notwendig. Es ist somit anzunehmen, dass dem zentralen Cannabinoidsystem eine bedeutsame Rolle bei der Kontrolle von Bewegungen zukommt. Möglicherweise liegt einzelnen Bewegungsstörungen eine Fehlfunktion in diesem Transmittersystem zugrunde.

Therapeutisch scheinen Cannabinoide insbesondere in der Behandlung hyperkinetischer Bewegungsstörungen sinnvoll eingesetzt werden zu können. Kontrollierte Studien zeigten eine signifikante Reduktion von Tics im Rahmen des Tourette-Syndroms und eine Minderung von Levodopa-induzierten Dyskinesien bei M. Parkinson. Darüber hinaus ergaben sich Hinweise auf Therapieindikationen bei Dystonien und einzelnen Tremorformen. Relevante Nebenwirkungen, die eine derartige Behandlung limitieren, traten in den bisherigen Untersuchungen nicht auf.

Der therpeutische Einsatz von antagonistisch wirksamen Cannabinoiden steht derzeit noch aus. Indikationen hierfür könnten sich in der Behandlung der Chorea bei M. Huntington sowie bei hypokinetischen Syndromen ergeben. Zweifelsohne sind vor einer abschliessenden Beurteilung weitere kontrollierte Studien mit grösseren Patientenzahlen notwendig. Die bisherigen Ergebnisse lassen jedoch vermuten, dass die verschiedenen Cannbinoide eine Erweiterung des therapeutischen Spektrums in der Behandlung von Bewegungsstörungen darstellen werden.

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Movement Disorders

Neurologic movement disorders are differentiated in hyperkinetic and hypokinetic conditions. Hyperkinetic disorders are characterized by involuntary movements such as tics, tremor, dystonia, myoclonus, and chorea. Patients suffering from hypokinetic (bradykinetic) disorders move too little which clinically results in parkinsonian features. Movement disorders are often associated with behavioral and/or cognitive changes. The underlying cause of the majority of these diseases is a dysfunction of basal ganglia-thalamocortical circuits. The 3 main transmitters used in the basal ganglia are glutamate (predominantly excitatory transmitter), gamma-aminobutyric acid (GABA, predominantly inhibitory transmitter), and dopamine. However, the pathophysiology of most diseases is not well understood. Many of them have a genetic basis with modification of phenomenology and course by environmental factors. Available symptomatic therapies are unsatisfactory by only suppressing involuntary movements or ameliorating hypo-/bradykinesia.

A better understanding of the functional organization of the basal ganglia, its excitatory and inhibitory inputs and associated modulatory systems should improve our knowledge of the pathophysiology of movement disorders and should result in improved therapeutic strategies.

Central Cannabinoid System and Movement Disorders

Central cannabinoid CB1 receptors have been found in the basal ganglia with high density on axon terminals of striatal efferent neurons projecting to the globus pallidus (GP) and substantia nigra pars reticulata (SNr) [15, 19] suggesting that cannabinoids regulate neurotransmission in the basal ganglia. Cannabinoid receptors are co-localized both with dopamine D1 receptors on striatonigral dynorphin/substance P containing neurons and with dopamine D2 receptors on striatopallidal enkephalinergic neurons [22]. Therefore, it has been suggested that cannabinoids might influence dopaminergic processes and might regulate motor activity [19, 22]. In addition, in the globus pallidus cannabinoid receptors are localized presynaptically on terminals of GABAergic input-neurons from the striatum [18]. Activation of cannabinoid receptors reduces GABA re-uptake in the lateral globus pallidus (GPl) [24]. There is much evidence that cannabinoids not only enhance GABAergic transmission in the GP but also regulate the activity of SNr neurons by presynaptic inhibition of GABA inputs [3, 28, 52]. There are cannabinoid receptors in the subthalamic nucleus (STN) as well. Recent reports suggested that cannabinoids inhibit the release of glutamate from the subthalamic terminals in the SNr [27, 48]. Furthermore, there is evidence for an interaction between the brain cannabinoid system and the endogenous central opioid system [36], the serotonergic system [20, 29] and the central cholinergic transmission [37].

Several animal studies support the hypothesis that cannabinoids modulate neurotransmission in the basal ganglia and regulate motor activity. Cannabinoids were found to potentiate neuroleptic-induced hypokinesia [30]. Repeated stimulation of dopamine D1 receptors enhanced cannabinoid-induced catalepsy [43]. Cannabinoid agonists were found to attenuate contralateral rotational behavior induced by a dopamine D1 agonist in rats with unilateral lesions of the nigrostriatal pathway [1]. Acute exposure to Δ^9-THC decreased the number of striatal D2 dopaminergic binding sites [42]. Perinatal exposure to cannabinoids altered the normal development of nigrostriatal dopaminergic neurons [40]. The cannabinoid receptor agonist (+)-WIN 55,212-2 exerts antidystonic effects in mutant dystonic hamsters [39]. In addition, it has been demonstrated that anandamide, identified as an endogenous ligand of the cannabinoid receptor [11], reduced locomotor activity [10, 44].

In summary, there is evidence of a general role of the endogenous cannabinoid transmission in the modulation of other transmitter systems within the basal ganglia mainly to limit the extent of glutamate activation and GABA inhibition [14, 41]. In addition, it is suggested that central CB1 receptors themselves are tonically active and therefore participate in the regulation of motor activity [2, 16].

In humans a limited number of clinical case reports and controlled studies are suggesting that cannabinoids might be useful in the therapy of movement disorders. Based on given experimental data and animal studies therapeutic strategies using cannabinoids predominantly focused on hyperkinetic movement disorders.

Gilles de la Tourette's Syndrome

Gilles de la Tourette's syndrome (Tourette syndrome, TS) is a complex neuropsychiatric disorder of unknown etiology, characterized by waxing and waning motor and vocal tics and a variety of associated behavioral disorders like obsessive-compulsive behavior (OCB), lack of impulse control, attention deficit hyperactivity disorder, anxiety, depression, and self-injurious behavior. It is suggested that basal ganglia circuits projecting to the frontal cortex and limbic regions are pathophysiologically involved. There is evidence that the dopaminergic system plays a role in TS pathology. Although the use of anti-dopaminergic drugs is commonly limited by side effects, neuroleptic drugs are the treatment of choice for symptomatic tic reduction.

Anecdotal reports suggested beneficial effects of marijuana (*Cannabis sativa*) in TS. Sandyk et al. [45] reported on 3 TS patients experiencing a significant amelioration (improvement of tic severity, urge to tic, self-mutilating behavior, attention span, and hypersexuality) when smoking 1/2–2 marijuana cigarettes per day. Hemming et al. [17] described a man who reported that he had been asymptomatic for more than one year when taking one 'cone' of marijuana per night.

We interviewed 64 TS patients about their use of marijuana and its influence on TS symptomatology. Of 17 patients reporting prior use of marijuana, 14 (82%) patients experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and OCB [32].

Therefore, we treated in an open uncontrolled pilot study 1 TS patient once with 10 mg Δ^9-THC, the major psychoactive ingredient of marijuana. The total tic severity score was 41 before treatment (measured by the Tourette's Syndrome Global Scale [21]) and 2 h after treatment was reduced to 7. Measuring cognitive functions, neuropsychological tests showed improved signal detection, sustained attention and reaction time after treatment. The patient himself noted an improvement of motor and vocal tics of about 70% and, in addition, felt an amelioration in attention, impulse control, OCB, and premonitory feeling without having any adverse reactions [35].

Therefore, we performed a randomized double-blind placebo-controlled crossover single-dose trial of Δ^9-THC in 12 adult TS patients. According to their body weight and prior use of marijuana, patients received 5.0, 7.5 or 10.0 mg Δ^9-THC. Using a self-rating scale (Tourette's Syndrome Symptom List [21]) there was a significant improvement of tics ($p = 0.015$) and OCB ($p = 0.041$) after treatment with Δ^9-THC compared with placebo. Different examiner ratings also demonstrated a marked reduction in mean tic scores. Statistical significance was reached for the subscore 'complex motor tics'. In addition, there was a definite trend towards a significant difference for the subscores 'motor tics', 'simple motor tics', and 'vocal tics'. No serious adverse reactions occurred. Five patients experienced transient mild side effects. Measuring cognitive functions, neuropsychological tests showed no significant differences after treatment with Δ^9-THC compared with placebo treatment in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance, and mood [31, 34].

In conclusion, we found that treatment of TS with Δ^9-THC is both effective and safe in the therapy of tics and probably associated behavioral disorders like OCB. We suggest that beneficial effects are due to a specific action on central cannabinoid receptors located in basal ganglia and hippocampus. Interestingly, neuroanatomical structures which are probably involved in TS pathology are heavily expressing the CB1 receptor system. Considering an involvement of the dopamine system in TS pathophysiology it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine mechanisms.

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by movement alterations (predominantly chorea but also dystonia, parkinsonism, and ataxia), behavioral changes and impaired cognition. Neuroanatomically there is a selective degeneration of 'medium size spiny neurons' in the striatum. In the early course of the disease there is an involvement of striatal GABA/enkephalin neurons projecting to the GPl. Later in the course there is also a degeneration of the GABA-substance P-containing striatal neurons projecting to the medial globus pallidus (GPm). In addition, a massive loss of cannabinoid receptor binding has been found in the SNr [15] and the GPl [38]. Symptomatic therapy of choreatic movements with anti-dopaminergic drugs is unsatisfactory in many patients.

A preliminary report suggested that cannabidiol (CBD), a major nonpsychoactive constituent of *Cannabis sativa*, is effective in reducing chorea in HD [46]. However, a placebo-controlled clinical trial in 15 neuroleptic-free patients who received 10 mg CBD/kg/day over a period of 6 weeks failed to demonstrate efficacy [5]. It can be speculated that CBD was ineffective either due to the massive loss of cannabinoid receptors in HD or due to the extremely low affinity of CBD for the cannabinoid receptor [38].

Therefore, we investigated whether nabilone, a synthetic cannabinoid agonist, would be effective in the therapy of HD. In an uncontrolled open clinical trial we treated a 58 year old male patient suffering from HD once with 1.5 mg nabilone. Using the chorea and the motor impairment scale by Folstein et al. [12], the chorea score was 10 and the movement impairment score 6 before treatment. Three h after treatment the chorea score was increased to 17 and the movement impairment scale to 13. On neurological examination there was a marked increase of choreatic movements at rest and during movement. This deterioration lasted more than 1 day (after 24 h chorea score was reduced to 12 and motor impairment score to 7) and completely disappeared within 2 days [33].

The marked increase of chorea under the treatment with nabilone could be either due to an enhanced GABA transmission in the GPm, or an activation of cannabinoid receptors located on striatonigral GABAergic neurons, or a decreased release of glutamate from the subthalamic terminals in the SNr, or an interaction with the dopaminergic system. It can be speculated that the activation of cannabinoid receptors did not enhance GABAergic transmission in the GPl and did not reduce choreatic movements because striatal neurons projecting to the GPl are already degenerated. It, therefore, can be hypothesized that cannabinoid receptor antagonists might be useful in symptomatic therapy of chorea in HD.

Dystonia

Dystonias are a heterogeneous group of neurological disorders defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures. Dystonia is classified by age of onset, etiology (symptomatic/idiopathic, sporadic/hereditary) and distribution (focal, segmental, hemidystonia, generalized). Dystonia is thought to be a disorder of the basal ganglia particularly the putamen and the thalamus. Symptomatic treatment includes local injections with botulinum toxin A, anticholinergic drugs and benzodiazepines. Particularly the treatment of generalized dystonia remains unsatisfactory in most patients.

Animal studies demonstrated that the cannabinoid receptor agonist (+)-WIN 55,212-2 exert antidystonic effects in mutant dystonic hamsters [39] and CBD was found to reduce torticollis in dystonic rats [6].

In humans anecdotal reports suggested beneficial effects of marijuana smoking and cannabinoids in dystonia [9, 25]. From uncontrolled single case studies it is suggested that CBD (200 mg, orally)

may be useful in the management of focal dystonia such as Meige's syndrome [50] and spasmodic torticollis [47] and of generalized torsion dystonia [47]. In another open uncontrolled trial of CBD in 5 patients suffering from dystonia oral doses of CBD (100–600 mg/day, over a period of 6 weeks) were found to reduce dystonic movements of 20–50% [8].

However, controlled studies are needed to assess whether cannabinoids are useful in the treatment of dystonic movements.

Parkinson's Disease and Parkinsonian Syndromes

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, resting tremor and postural instability. Pathophysiologically it is characterized by a depletion of dopamine in the striatum resulting in an increased inhibitory GABA basal ganglia output. Therapy of PD includes levodopa, dopamine agonists and surgical procedures. PD has to be differentiated from other parkinsonian disorders which share some clinical features with PD. However, parkinsonian syndromes differ in the underlying pathology which is thought to be a decreased density of postsynaptic dopamine receptors. PD and other parkinsonian disorders are summarized as hypokinetic movement disorders.

In an open uncontrolled study of CBD in dystonia in 2 patients with 'coexisting parkinsonian features' an exacerbation of hypokinesia and resting tremor was observed while dystonic movements improved [8]. Another open clinical trial in 5 patients suffering from PD failed to demonstrate any beneficial effect on tremor or other parkinsonian symptoms when smoking a marijuana cigarette [13].

However, a single case study suggested that CBD may be effective in the management of levodopa-induced dyskinesia in a PD patient [51]. Accordingly, in a double-blind placebo-controlled crossover study in 7 PD patients it has been demonstrated that oral nabilone reduces levodopa-induced dyskinesias without aggravating parkinsonism [49]. In PD dyskinetic side-effects are a main problem after prolonged treatment. It is thought that dyskinesia is caused by an overactivity of the GPI. Data obtained from the reserpine-treated rat model of PD suggested that cannabinoids might act to reduce D_2-mediated reductions in GABA release in GPl [23]. Therefore, it has been suggested that nabilone may reduce levodopa-induced dyskinesia due to a reduction of GABA re-uptake in the GPl [49].

In summary, there is some evidence that in PD accompanying treatment with cannabinoids is useful to reduce the complications of dyskinesia after prolonged levodopa therapy without aggravating parkinsonian symptoms.

Tremor

Tremor is defined as a rhythmical, involuntary oscillatory movement of a body part. It can be classified clinically (rest, postural, simple kinetic, and intention tremor). Numerous etiologies for tremor are known and different pathways have been suggested to be involved in tremor. Pharmacologic treatment of tremor often remains unsuccessful.

In Parkinson's disease and other parkinsonian syndromes it is unclear whether cannabinoids change resting tremor [8, 13, 49].

In patients suffering from multiple sclerosis (MS), tremor is a common clinical phenomenon. Using a questionnaire, 112 MS patients reported some alleviation of their symptoms including tremor with cannabis use [7]. In a placebo-controlled single-blind trial, 2 of 8 MS patients demonstrated an improvement in seriously disabling tremor after Δ^9-THC treatment (5–15 mg) [4]. In addition, a case study of a 30-year-old man suffering from MS showed an improvement of hand action tremor while he smoked a marihuana cigarette [26]. Additionally electromagnetic recordings revealed an almost completely abolished hand-and-finger tremor after smoking.

From the available clinical data it remains unclear whether cannabinoids are useful in reducing tremor. Further studies considering different forms of tremor are needed.

Conclusions

Several investigations demonstrated that cannabinoids modulate neurotransmission in the basal ganglia by increasing GABAergic transmission, inhibiting glutamate release and affecting dopaminergic uptake. These results suggested that cannabinoids might be of therapeutic value for movement disorders. Clinical trials in humans showed that cannabinoids are effective in the treatment of hyperkinetic movement disorders such as levodopa-induced dyskinesia in PD, tics in Tourette syndrome, some forms of tremor, and dystonia. However, further placebo-controlled, double-blind studies are needed to confirm the efficacy of cannabinoids and which of the different cannabinoids (e.g., Δ^9-THC, CBD, nabilone) will be the most effective in the treatment of movement disorders. Present clinical data do not show serious side effects. It can be speculated that cannabinoid receptor antagonists could be useful in the treatment of hypokinetic movement disorders such as PD and parkinsonian syndromes and of chorea in HD.

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