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Dopamine D_2-receptors in human narcolepsy: a SPECT study with ^{123}I-IBZM

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Increased dopamine D_2 receptor binding in basal ganglia has been reported in human narcolepsy. These studies have been based on post-mortem material of 8 patients, most of them also medicated for narcolepsy. We studied six narcoleptics without stimulant or anticataplectic medication. The patients had an unambiguous history of cataplexy, and they were also studied polygraphically. Single photon emission computed tomography (SPECT) imaging was performed. The D_2 receptor density was determined by using ^{123}I-iodobenzamide (IBZM). The control subjects were 8 unmedicated Parkinson patients with one-sided (hemiparkinsonian) clinical symptoms. The D_2 receptor density in them is known to be normal or somewhat increased compared to healthy normals. The striatum/frontal D_2 activity ratio was 1.331 ± 0.084 (with phantom study correction 2.101 ± 0.300) in the narcoleptic patients, and in the parkinsonian controls 1.321 ± 0.052 (2.067 ± 0.185) for the asymptomatic side and 1.335 ± 0.025 (2.117 ± 0.090) for the symptomatic side (i.e. contralateral to the side with the clinical extrapyramidal signs). There was no statistical difference between the groups or between the symptomatic and asymptomatic side in the Parkinson patients. Thus, our results differ from the earlier post-mortem studies.

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Narcolepsy is a relatively rare, chronic, usually idiopathic sleep-wake disorder causing excessive daytime sleepiness, irresistible sleep attacks, cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep (1). There is evidence of dopaminergic mechanisms being involved in sleepiness and sleep attacks in narcolepsy. Reduced levels of dopamine (2) and its metabolite homovanillinic acid (HVA) (3) in the cerebrospinal fluid have been found. The most effective alerting drugs (amphetamines and methylphenidate) enhance dopaminergic transmission in the brain (4).

Recently, neurochemical changes in post-mortem material have been reported in human narcolepsy. In cerebral cortex a reduction of α_1 receptors but an increase of noradrenaline and serotonin metabolites has been observed (5). In basal ganglia α_2 receptors were increased (6). Striatal dopamine and HVA were normal (5). Results on the dopamine D_1-receptor binding were contradictory: both normal (5) and increased (about 55%) levels in caudate and medial globus pallidus (7) have been reported. Results of D_2 binding have been more consistent. In one study an 125% increase in caudate and putamen was reported (5). In another study increases in caudate (63%), lateral globus pallidus (95%) and lateral amygdala (93%), but not in putamen were found (7).

The canine model of narcolepsy is clinically similar but not neurochemically identical with human narcolepsy (4, 8–10). The D_2 receptor density is increased in the amygdala, rostral caudate, and nucleus accumbens (10). D_2 antagonists suppress and D_2 agonists aggravate cataplexy, and the effect is believed to be mediated presynaptically or via the noradrenergic systems (11).

^{123}I-iodobenzamide (IBZM) has a high specific binding to D_2 postsynaptic receptors in the striatum (12). The binding to various brain structures, e.g. frontal cortex, is non-specific and can thus be used as an internal reference for demonstrating changes in the specific striatal binding. The ratio of striatal *vs* frontal cortical binding is a measure of D_2 receptor density (13). We have assessed the D_2 receptor density using IBZM-SPECT in living narcoleptic patients without medication for narcolepsy.

Material and methods

Subjects were six patients (mean age 39.7 and range 20–57 years, five women) with narcolepsy (mean

deviations. As statistical method was used analysis of variance.

Results

The striatum/frontal D_2 activity ratio was 1.331 ± 0.084 (with phantom study corrected values 2.101 ± 0.300) in the narcoleptic patients, and in the parkinsonian controls 1.321 ± 0.052 (with correction 2.067 ± 0.185) for the asymptomatic side and 1.335 ± 0.025 (with correction 2.117 ± 0.090) for the symptomatic side (i.e. contralateral to the side with the clinical extrapyramidal signs; see Table 2). There were no statistically significant differences between the groups nor in the side-to-side differences.

Discussion

We found no consistent increase in the number of dopamine D_2 receptors of living patients measured with iodobenzamide (IBZM) using single photon emission computed tomography (SPECT). Our results are in contrast with two recent studies (5, 7) in which ^{3}H-spiperone labelling in narcoleptic autopsy material was used. Methodological differences may partly explain the discrepancy. Although ^{3}H-spiperone has a high affinity for D_2 receptors it also binds to serotonin 5HT-2 receptors (19) and to so-called spirodecanon sites (20). IBZM has a high selectivity for D_2 receptors, and the results are not totally comparable with those made with ^{3}H-spiperone (18). There may also be differences in the D_2 expression of living and dead cells. However, there are also other factors which may be of importance.

Medication used prior to death probably affects the binding results (6, 7, 18). Of the eight post-mortem subjects reported by Kish et al. (5) and Aldrich et al. (7), three had used d-amphetamine, three methylphenidate, one had been drug-free, and in one the drug status was unknown. Chronic d-amphetamine treatment decreases ^{3}H-spiperone binding in rat striatum (21) but increases binding in cat striatum (22). Depletion of dopamine and loss of dopamine uptake sites in rat brain follows repeated administration of d- and methylamphetamine, but not after methylphenidate either in rat or in monkey brain (23). Thus, the effect of previous medication on the dopaminergic system is difficult to assess as its duration is not known, and there might also be species- and drug-specific differences. Because all our patients had no medication for narcolepsy (or other medication known to affect the dopaminergic system), it can be assumed that our results reflect a genuine D_2 receptor status, not modified by drug use.

It may also be speculated that the duration of the disorder and the age of the patient may affect receptor densities. The symptoms in narcolepsy usually evolve over a few years but later on the symptoms reflecting abnormal REM sleep regulation (cataplexy, sleep paralysis and hypnagogic hallucinations) may disappear spontaneously in 20–40% (24) or improve in up to half of the patients (25). This alleviation of symptoms may be due to a gradual change in the balance of the neurochemical regulation systems. In the post-mortem subjects (5, 7), the duration of narcolepsy was >20 years in 6/8 and only one subject was <40 years old. Among our patients both the age and the duration are more variable. Interestingly, D_2 binding was highest in narcolepsy Patient 2 who also had the shortest duration of the disorder. Thus, receptor densities might differ in novel and long-standing narcolepsy.

Neurochemical studies are critically dependent on the diagnostic accuracy of the subjects or material investigated. Although there are detailed diagnostic criteria (1) the diagnosis of narcolepsy can be problematic (26). Recently it has been shown that the history of cataplexy is a better discriminant of narcolepsy than the number of sleep onset REM (SOREM) periods on a single multiple sleep latency test (MSLT) (26). Moreover, the number of SOREMs is variable even in the same patients in different recording situations (27). Although Patients 5 and 6 had less than two SOREM periods on the MSLT as required in the current diagnostic criteria (1), we consider the narcolepsy diagnosis also reliable in these two, based on the demonstration of clearly abnormal sleepiness (mean sleep latencies 2.5 and 3.0 min, respectively) and a convincing history of cataplexy. As increasing numbers of HLA DR2 negative narcoleptics have been found, the differential diagnostic value of HLA typing has also become limited (26) – especially in populations with high DR2 frequency (e.g. in Finland 34%). Therefore, we have not systematically performed tissue typings in our narcoleptics.

Of the post-mortem patients all three in the study by Kish et al. (5) had cataplexy but only one was polygraphically examined. In the study by Aldrich et al. (7) 3 of 5 subjects had a reliable history of cataplexy, and 2 of these 3 had SOREM, but no information was given about the number of SOREMs or about sleep latencies. The D_2 binding was lower in the subjects with definite cataplexy (7). Consequently, 1/3 patients in Kish et al. (5) and 2/5 patients in Aldrich et al. (7) had a REM-related symptom (cataplexy) *and* were polygraphically examined as the current diagnostic criteria require (1). Still, the particular patient of Kish et al. (5) also had a marked hydrocephalus caused by a subependymoma in the brain stem, making it difficult to generalise the results of this patient to patients with idiopathic narcolepsy.

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In our study the use of Parkinson patients as controls has theoretical drawbacks, but we had no opportunity to investigate healthy normals with IBZM-SPECT because of limited economical resources. However, in our opinion when regarding the practical implications, this control material does not invalidate the results. In unmedicated parkinsonian patients there has been no significant changes in IBZM-SPECT binding ratios compared to controls (17, 28). The results using another D_2 ligand ^{11}C-raclopride in PET studies have given normal or mildly (maximally 34%) increased D_2 receptors (27). Thus, despite some limitations caused by our control material, D_2 receptor binding increases of the order reported in the post-mortem narcolepsy studies (63–125%) (5, 7) should have been observed in our narcoleptic subjects.

In conclusion, we cannot confirm the previously reported increase in D_2 binding in the basal ganglia of narcoleptics. However, the number of patients is relatively small also in our study, there were considerable interindividual differences, and we used different methods. Generally, the neurochemical studies in narcolepsy deal with several uncompletely known variables, and a major difficulty is also the acquisition of sufficient and representative material. To solve these problems further detailed studies are needed, preferably on unmedicated patients with different durations of unequivocal narcolepsy.

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