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Dopamine D_2 receptor alteration in patients with periodic movements in sleep (nocturnal myoclonus)

Short Communication

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Summary. Periodic movements in sleep (PMS) can cause severe sleep disturbances. We investigated the central dopamine D_2 receptor density in patients with PMS with ^{123}I-IBZM and single photon emission tomography (SPET). In PMS there was a lower ^{123}I-IBZM *binding* in the basal ganglia compared to *the control group*. The results indicate a loss of central D_2 receptors in PMS.

Keywords: Dopamine receptors, nocturnal myoclonus, PMS, SPET.

Introduction

The nocturnal myoclonus (Periodic movements in sleep = PMS) are stereotyped, repetitive jerks of the lower limbs that can occur during sleep. PMS is often related with restless legs (RLS) (Montplaisir et al., 1985) and can cause severe sleep disturbances and daytime sleepiness. Prevalence positively correlates with age and is affecting up to 45% of subjects aged 65 or older (Ancoli-Israel et al., 1985; Coleman, 1982). Recently two controlled studies showed the efficacy of *dopamine agonists* in the treatment of PMS (Brodeur et al., 1988; Walters et al., 1988). The worsening of PMS by pimozide, a dopamine antagonist (Akpinar, 1982) and by gamma hydroxybutyrate, a blocker of dopamine release (Montplaisir et al., 1986; Roth et al., 1973) supports the hypothesis of a decreased dopaminergic activity in CNS. High levels of free dopamine and homovanillic acid (HVA) in the cerebrospinal fluid of one patient with PMS (Montplaisir et al., 1985) indicate no decrease in biosynthesis, but suggest an impared sensitivity or a loss of postsynaptic dopamine receptors. In this study we applied ^{123}I labeled 3′-iodo-6-methoxybenzamide (IBZM) (a highly selective CNS D_2 dopamine receptor ligand) and single photon emission tomography (SPET) in

12 patients. *Until now* six patients got a second SPET investigation after a 3 month therapy with *dopamine* agonists to investigate whether striatal D_2 receptor density is altered in PMS and whether there is a receptor-regulation after treatment that possibly correlates with the therapy response.

Method

Twelve patients [3 women, 9 men, mean age 56.3 (37–79) years] and *four* control subjects [*2 women* (52 y, *57 y*), 2 men (25 y, 59 y)] were examined. Informed consent was obtained. Eight patients suffered from PMS combined with RLS, four from PMS alone. All-night polysomnographic recordings (PSG), including EMG of ant. tibialis muscles were performed for 2 consecutive nights. In addition to the standard EEG criteria (Rechtschaffen and Kales, 1968) the total number of phasic EMG activity per hour of time spent in bed (PMS-index) was scored. In order to study the effect of a 3 month *dopamine agonist* administration on striatal D_2 receptors, five patients started with 62,5 mg L-Dopa per night, one patient received 20 mg Bromocriptine per night. The L-Dopa dose was increased to a maximum of 375 mg according to the response and/or the presence of side effects. In order to ascertain drug-free control SPET after the 3 month treatment, the patients were withdrawn 48 h before the second investigation.

The SPET was performed after 90 min i.v. administration of the radiopharmaceutical. According to other investigators (Brücke et al., 1991; Costa et al., 1990) and the manufacturer (Cygne BV) an activity dose of 185 MBq ^{123}I-IBZM was administered intravenously per patient. For acquisition a rotating gamma camer (Picker International) connected to a PCS 512 computer (Picker FRG) was used. A series of 64 images were collected at 6° increments for 30 s each into a 64 × 64 pixel matrix. In order to ascertain an exact reconstruction, the orbitomeatal line (OM-line) was delineated externally by using two radioactive point sources at the end of the acquisition. Transverse slices were corrected into the OM-line and attenuated by a method developed by us. Standard regular regions of interest (ROI's) were drawn on the basal ganglia (BG) on each hemisphere (size 42 pixels) and irregular ROI's were drawn around the brain contour (Cx) by using the 30% threshold in the OM-line +36 mm. *The irregular 30% threshold ROI determination around the brain slice contour is in comparison to frontal reference ROI's easily performed, especially in cases with lower binding of the tracer in the BG and enhancement of surrounding cortical structures, but has the potential disadvantage that the BG/Cx ratios could be influenced by enlarged ventricles and by brain atrophy. On the other hand age related brain atrophy would induce higher ratios. The physiological age-related decline in receptor density would be less pronounced by this method. This could be of potential advantage concerning age-matching. The BG/Cx activity ratios were determined as followed:*

$$\mathrm{BG/Cx} = \frac{\mathrm{BG\,(average)}}{\mathrm{Cx - BG}}$$

The ratios were expressed as mean and the obtained data were compared by the *non-parametric Wilcoxon rank-sum test.*

Results

The SPET of normal controls showed hot spots within *the striatal regions* and a low ground activity of the surrounding brain. The mean BG/Cx ratio of the controls was 1.54 (range 1.51–1.59) (Fig. 1). In PMS patients there was a lower contrast between BG and Cx. The mean BG/Cx ratio was 1.39 (range 1.19–1.49) and significantly smaller compaired to the control group ($p = 0.004$, Fig. 1). After the treatment the BG/Cx ratios remained unchanged in four, and an increase was seen in one therapy-responder and in one non-responder.

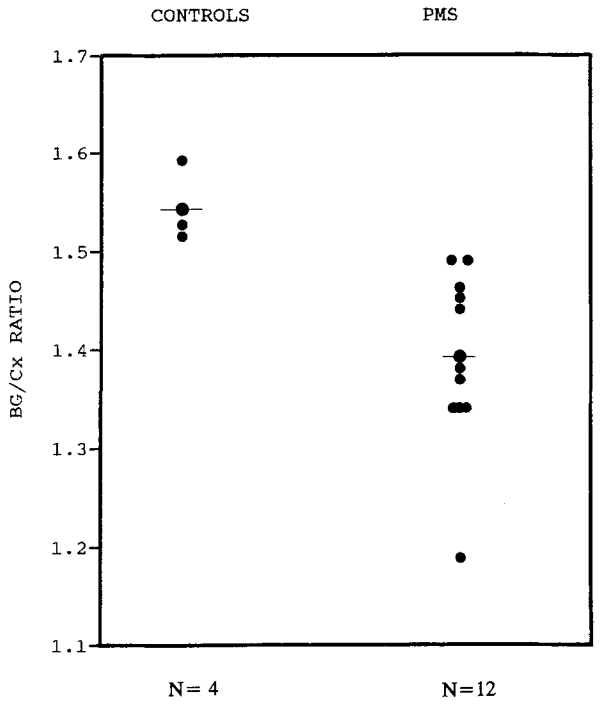

Fig. 1. Distribution of BG/Cx ratios of patients and normal controls (mean: —●—)

Conclusion

In comparison to the control group we found a significant reduction of the BG/Cx ratio in PMS. *The lowest tracer binding was found in the most sleep disturbed patients, but to date the number of patients is to small to establish clear correlations with the course of treatment. The D_2 receptor upregulation after the treatment is surprising, because we expected a downregulation. The upregulation points to a disturbance of the corticostriatal afferents in PMS. This is underlined by animal (rats) experiments, in which a hemidecortication and following d-amphetamine treatment leeds to a striatal D_2 receptor upregulation at the lesioned and to a downregulation at the intact side (Robertson, 1986).*

The mean BG/Cx ratio of the controls confirmed results by Tatsch et al. (1991), whereas the low *binding* of ^{123}I-IBZM in BG in PMS seems to be similar to results in schizophrenic patients on anti-psychotic drugs (Costa et al., 1990; Verhoeff et al., 1990) and in patients with Huntington's disease (Brücke et al., 1991). Therefore the results indicate a loss of D_2 receptors on PMS. *According to animal investigations D_2 receptors are not only localized on GABAergic neurons, a relatively large subpopulation (about 40%) seems to be localized on cholinergic interneurons in the BG (Dawson et al., 1988). Therefore, from our point of view, further studies on more patients should focus on the corticostriatal glutamatergic and cholinergic-dopaminergic interactions in this disease.*

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