TOTAL SLEEP DEPRIVATION AND PARKINSON DISEASE

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A major problem in the long-term management of Parkinson disease (PD) is the progressive loss of efficacy of L-Dopa, an effect attributed, at least in part to diminished responsiveness of dopaminergic receptors in basal ganglia [14]. The restoration of normal responsiveness or the induction of receptors hypersensitivity would be valuable not only in the management of L-Dopa therapy complications, but also as a treatment of PD. It is known, since the work of Ferguson & Dement (1969) that rapid eye movement sleep deprivation (REM SD) enhances the aggressive behavior induced by amphetamine [8]. This effect, first attributed to either norepinephrine or serotonin, was later demonstrated to be dopamine dependent, at least in part. Thus, it was shown that REM SD enhances aggressive behavior induced by apomorphine, a powerful agonist of dopaminergic receptor [5,16]. Further studies demonstrated the same effect for the stereotyped behavior induced by apomorphine [24]. Aggressive behavior was also observed in nomifensine, piribedil and bromocriptine-treated rats after REM SD [6,22], again suggesting dopaminergic system participation. These evidences taken together suggest that an effect of REM SD could be the induction of hyperresponsiveness to dopaminergic agents. In this respect, it is pertinent that in rats with an experimental model of PD obtained by bilateral lesion of nigrostriatal pathway, REM SD improved ambulation and rearing [1]. It is well known that in PD there is a dopaminergic deficiency in the nigrostriatal system (for a review of the subject see Hornykiewicz [11] and Rinne [20]). A less appreciated point is the role of CNS dopaminergic systems in depression: although data are often conflicting, several investigators reported lowered levels of 5-hydroxyndolacetic acid (5HIAA), homovanilic acid (HVA) and 3-methoxy--4-hydroxyphenilglycol (MHPG), respectively major metabolites of serotonin, dopamine and norepinerphrine, in cerebrospinal fluid of depressed patients [2,7,18]. Similar trends were observed with the urinary excretion of cathecolamines and their metabolites [21]. Several antidepressant drugs, including nomifensine, exhibit a rather potent inhibition of dopamine uptake in brain [9,19,29]. Therapeutic trials of L-Dopa in depressive patients were benefitial, specially in the cases with

retarded behavior and low motor activity [4,25], although this response was not observed by other researchers [12]. In another line of investigation there has been an increasing number of papers showing that total [3,13,17] or selective REM SD [26-28] brings a significant, although transitory, improvement to depressed patients.

These data led us to study the effects of one night of total SD on patients with PD.

MATERIAL AND METHODS

Patients — Twelve parkinsonian patients were included in the experiment. Diagnosis of PD was based on the presence of at least three clinical signs: bradykinesia, rigidity and posture and gait disturbances. All the volunteers had a diagnosis of idiophatic PD, age ranging from 40 to 70 years, and a score for parkinsonian syndrome from 20 to 50% by the New York University Parkinson's disease evaluation form (NYU form) [15]. No patient had history of any other neurological disorder, previous exposition to manganese, neuroleptics and other drugs known to induce parkinsonian syndrome. All patients signed an informed consent, after being explained in details about the experimental protocol, care being taken in order to avoid describing the expected therapeutic effect, so that an undesired placebo effect was avoided.

Procedure — After admission to the protocol, the patients were maintained for at least two weeks with their medication unchanged. They were then admitted to a special ward at the Medical School Hospital, where they had contact only with the research staff. The admittance day was considered day 0. At 5:00 PM the patients were evaluated using the Hamilton Rating Scale for Depression (HRSD) [10] followed by the NYU form. The patients were instructed to go to bed on that evening and to awake in the next morning at their usual time. The patients remained all day 1 in the Hospital and at 5:00 PM they were again evaluated using both rating scales. At 9:00 PM the patients were removed to an isolated Clinical Research Unit to spend the night awaken. The Unit was composed by a visiting room and a bathroom, with a TV set, ambiental music and game sets (like chess and playing cards). Patients were instructed not to drink coffee or other stimulant beverages and not to smoke. The procedure was done with groups of 2 or 3 patients under close supervision of 2 members of our staff. At morning of day 2 the patients returned to the special ward and at 10:00 AM were evaluated by the NYU form (except appendix 6). At 5:00 PM they were evaluated again using both rating scales. After that they were discharged, with instructions to return at 5:00 PM on day 8, 15 and 29 when both rating scales were again applied. The rating scales were applied by an independent researcher who was beforehand aware of the protocol conditions, that is, the experiment was not run blind, because of its own peculiarities. In fact, in the first phase of the clinical interview the patients spontaneously reported his previous sleep deprivation. On the other hand, video taped examinations would not be applicable taking into consideration all the items of the NYU form.

The HRSD was modified so that items 7 (work and activities), 9 (agitation), 13 (general somatic symptoms) were excluded as to cope with disability of the patients. Item 17 (insight) was also excluded as the PD patients have a clear insight of their own disease. Therefore the maximum score for the remaining 13 items was 40 points, instead of the original 53. The NYU form was applied according to the author's instructions [15].

Results were analysed by comparing the scores at day 0 (afternoon of admission) with data obtained at day 1 (after a night sleep in the Hospital), to verify the possible influence of hospitalization on symptomatology of PD, using the Friedman test.

Using the same test, a comparison was done of the data obtained at day 0 (afternoon before deprivation) with data collected at days 2, 8, 15 and 29, so that it was possible to assess the influence of sleep deprivation on the clinical picture of PD.

RESULTS

Table 1 summarizes personal data of the 12 patients. They were in average 61 years old, with a median disease duration of 5.1 years. All were under medication, either anticholinergics (patients 1, 2, 8 and 12) or L-Dopa (patients 3, 9, 10 and 11) or the combination of both drugs. Comparing the total scores for both rating scales days 0 and 1 disclosed no statistical significant differences, indicating that hospitalization did not influence the symptomatology of PD (Table 2). Comparison of day 0 with days 2, 8, 15 and 29, however, disclosed statistically significant results. As it can be seen, values at day 0 differ significantly from 2, 8, 15 for rigidity, bradykinesia, gait and posture disturbances and functional disability evaluation. On day 29 these variables showed values still lower than those seen at day 0, although the differences did not reach statistical significance. As also seen in Table 2, tremor was not influenced by SD, as the scores after SD did not significantly differ from values obtained at day 0. It must be stressed that 5 patients did not display tremor in their symptomatology, therefore the data on Table 2 are from the remaining 7 patients. Abnormal involuntary movements (NYU form appendix 5) were not taken into account as only 3 of the patients had such movements and statistical data based on such small population would be meaningless. It was noted that these 3 patients had an increase of their involuntary movements on the day after SD, although they claimed it was easier to walk and to use the hands. Aside from the clear improvement detected by the NYU form items, the examiners had a subjective impression that the patients displayed an overall better functional ability on the day following SD. Such impression was confirmed by the reports of the patients and their relatives. For example, patient 1 was taken to the Clinical Research Unit on a wheelchair, and on the day after SD was able to walk unaided; patient 10, who needed support

Patient	Age (years)	Disease duration (years)	Medication - daily dose
1	68	1.5	BPD - 4 mg
2	50	4	THF - 4 mg
3	63	12	CB/LV - 62.5/625 mg
4	69	6	THF - 6 mg; CB/LV - 62.5/625 mg
5	65	4	BPD - 6 mg; BZ/LV - 150/600 mg
6	51	5	BPD - 6 mg; CB/LV - 25/250 mg
7	50	3	BPD - 6 mg; CB/LV - 75/750 mg
8	70	1.5	BPD - 4 mg
9	56	2	CB/LV - 50/500 mg
10	63	10	CB/LV - 175/1750 mg
11	68	8	CB/LV - 50/500 mg
12	58	5	THF - 5 mg

Table 1 — Age, disease duration and medication of 12 parkinsonians submitted to total sleep deprivation. BPD, biperiden; THF, trihexyphenidyl; CB/LV, carbidopa/levodopa; BZ/LV, benzerazide/levodopa.

to walk before SD, after it was able to walk alone, although there was a clear worsening of the involuntary movements induced by L-Dopa. Figure 1 shows the effect of SD on depressive symptoms and on the general score for PD. Improvement of parkinsonian symptoms remained for 2 weeks, while depressive symptoms at day 15 were no longer significant from day 0.

Day	0	1	2	8	15	29
Rigidity	39.2(37.8)	40.0(39.2)	22.8(22.1)*	27.1(26.4)*	29.2(24.9)*	35.6(29.3)
Tremor (a)	28.5(33.2)	30.0(30.7)	21.4(29.2)	20.0(20.7)	18.5(22.1)	21.4(22.1)
Brady-kinesia	48.7(45.0)	51.2(47.5)	36.2(32.5)*	32.5(28.7)*	40.0(36.2)*	40.0(35.0)
Gait & Posture	37.7(33.2)	42.2(38.8)	18.8(22.2)*	20.0(15.5)*	21.1(19.9)*	20.0(28.8)
Func. Disability	29.0(23.1)	22.0(24.8)	12.5(12.4)*	13.5(11.1)*	14.5(12.5)*	20.6(17.5)
General Score	29.6(28.1)	31.3(27.9)	20.2(19.9)*	17.4(17.2)*	17.6(18.5)*	23.2(24.0)

Table 2 — Median of the scoring of parkinsonian symptoms before and after a single night of total sleep deprivation. (a) for tremor n=7, for all other variables n=12; ( ) semi-interquartile range; * asterisks indicate statistically significant difference (Friedman test; p ≤ 0.05) in comparison to day 0.
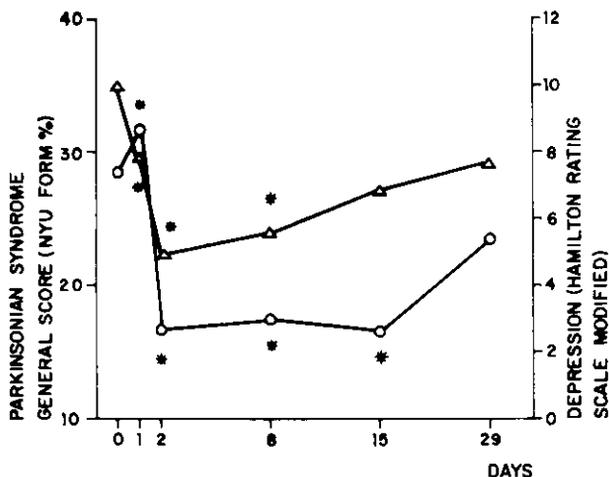

Fig. 1 — Depressive symptoms (triangles) and PD general score (circle) before and after a single night of sleep deprivation (arrow). Asterisks indicate statisticaly significant difference in comparison to day 0.

COMMENTS

SD revealed to be a simple and well tolerated procedure by all patients involved in this study.

Improvement in depression in our patients did not differ greatly from the results obtained in non-PD depressive patients reported elsewhere, either with total [3,13,17] or selective REM SD [26-28]. Benefits, like in our patients were short-lived and tentative explanations for the results observed were accumulation at relevant brain sites of a catecholamine or its metabolites, which could alleviate depression [26] or resynchronization of disturbed biological rythms [17]. In our patients a point could be raised that depressive symptoms improved as a consequence of PD improvement, but this is hardly tenable, as PD symptoms mantained the lower scores for a longer period a mean of 2 week (or even longer for some patients) — against just one week for depressive symptoms.

As far as PD symptomatology is concerned, the result obtained indicate a positive response to SD, which was mantained for at least 2 weeks. Thus, SD has a beneficial effect 'per se' or was able to potentiate the effects of the drugs used by the patients. However the latter possibility is less likely, as the patients were using different therapeutic schedules, involving drugs with different mechanisms of action. A placebo effect seemed also not to be involved as the patients were not told that an improvement could occur after SD. Furthermore it would be difficult to explain a placebo effect acting not only on functional disability rating scale, but also on objective parameters of the rigidity, bradykinesia and gait and posture disturbance and, at the same time, with a very slight action on tremor. It should also be mentioned the worsening of the L-Dopa dyskinesias caused by SD in 3 patients.

A tentative explanation for the results is that SD may act directly on dopaminergic receptors. REM SD increased aggressive behavior induced by dopaminergic agonists [22]; the use of alpha-methyl-p-tyrosine failed to modify the exagerated apomorphine response in the REM SD rats, and merely increasing brain concentration of dopamine did not enhanced apomorphine effects [23]. All these findings point to a dopamine receptor mediated effect leading to the hyperresponsiveness to apomorphine observed in the SD animals.

The possibility that SD acts directly on the dopaminergic receptors is only an speculation at the moment. Although REM SD rats have shown all the above changes in responsiveness to dopaminergic agents, there are not data at present demonstrating the receptor changes. Although the mechanism of improvement presented by our patients remains unexplained, the results obtained indicate that SD may be an useful and harmless therapeutic procedure in PD.

SUMMARY

Twelve Parkinson disease (PD) patients were submitted to a single night of total sleep deprivation (SD). Disease duration had a median of 5.1 years and all were using either anticholinergic or L-Dopa or the combination of both drugs. After SD there was an improvement of rigidity, bradykinesia, gait and

posture disturbances and functional disability that remained significant for 2 weeks. No effect was observed on tremor. Concerning depressive symptoms, a significant difference was noted, that remained for one week. These results suggest that SD may be an useful procedure to improve PD symptomatology. It is discussed a possible change of dopaminergic receptors, induced by SD, to explain the improvement.

RESUMO

Privação de sono total na doença de Parkinson.

Doze pacientes com doença de Parkinson (DP) foram submetidos a privação de sono total. A média de idade dos pacientes era 61 anos e a duração da doença era em média de 5,1 anos (1,5 a 12 anos). Quatro deles usavam apenas anticolinérgico, 4 usavam L-Dopa e 4 combinação de drogas de ambos os grupos. Após privação de sono total por uma única noite foi verificada melhora na rigidez, bradicinesia, alterações de postura e marcha e incapacidade funcional com duração de duas semanas, em comparação com os escores quando da inclusão no estudo. Não foi observado efeito sobre o tremor. Em relação aos sintomas depressivos foi verificada melhora com duração de apenas uma semana. Estes resultados sugerem efeito benéfico da privação de sono na DP. Com base em estudos experimentais julgamos que uma explicação possível para estes resultados seja a modificação de receptores dopaminérgicos.

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