Depression in Parkinson's Disease Is Not Accompanied by More Corticotropin-Releasing Hormone Expressing Neurons in the Hypothalamic Paraventricular Nucleus

Witte J.G. Hoogendijk, Jan S. Purba, Michel A. Hofman, Rob A.I. de Vos, Ernst N.H. Jansen, and Dick F. Swaab

Background: Depression is frequently encountered in Parkinson's disease (PD). In addition, more than half of the PD patients have a disturbed dexamethasone suppression test, which is associated with increased activity of corticotropin-releasing hormone (CRH) neurons. We recently found an increase in CRH neuron number, CRH-messenger RNA, and vasopressin colocalization in CRH neurons in the paraventricular nucleus (PVN) of depressed patients, which may be involved in the pathogenesis of depression.

Methods: The number of neurons expressing CRH was determined in the PVN of 6 depressed PD patients with a high score (≥ 13) on the Hamilton Depression Rating Scale, 6 nondepressed PD patients, and 6 controls.

Results: The three groups did not differ in the number of neurons expressing CRH.

Conclusions: We hypothesize that activation of CRH neurons in the PVN, as we recently observed in idiopathic depression, does not play an essential role in depression in PD. Biol Psychiatry 1998;43:913-917 © 1998 Society of Biological Psychiatry

Key Words: Depression, Parkinson's disease, dementia, corticotropin-releasing hormone, paraventricular nucleus, hypothalamus

Introduction

Depression symptoms are frequently encountered in Parkinson's disease (PD; Cummings 1992), but their type and clinical course are different from the symptoms

in idiopathic depression (Mayeux et al 1984). Nonsuppression following dexamethasone frequently occurs in PD patients, which indicates increased activity of corticotropin-releasing hormone (CRH) neurons (Rabey et al 1990). CRH neurons are located in the paraventricular nucleus (PVN) of the hypothalamus and stimulate the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which stimulates cortisol secretion from the adrenal cortex. CRH might be causal in depression, not only because hypothalamic-pituitary-adrenal (HPA) endocrine activity is increased in depression (Holsboer et al 1992), but also because CRH neurons project into the brain, and because in animal experiments intracerebroventricular administration of CRH leads to signs of depression, e.g., decreased food intake, decreased sexual activity, changed motor behavior, and disrupted sleep patterns (Holsboer et al 1992). Furthermore, we recently found a strong hyperactivity of CRH neurons in the hypothalamic PVN in autopsy material from depressed patients. This hyperactivity was indicated by the fourfold increase in the number of neurons expressing CRH, the increased colocalization of CRH and vasopressin, and the increased amount of CRH-messenger (m)RNA (Raadsheer et al 1994a, 1995). Moreover, antidepressants normalize the increased concentration of CRH in the cerebrospinal fluid of depressed patients (De Bellis et al 1993) and decrease CRH-mRNA in the PVN of rats (Brady et al 1992). To determine whether depression in PD is also accompanied by CRH neuron activation, we measured the number of CRH-expressing neurons in the PVN of the hypothalamus of PD patients with and without depression.

Methods and Materials

Thirty-three patients with idiopathic PD were included in a follow-up study on clinicopathological correlates in PD (de Vos et al 1996), following written informed consent. Patients were evaluated every 6 months, including complete medical, neurological, and psychiatric examinations. Mood disorders were

From the Graduate School Neurosciences Amsterdam, Netherlands Institute for Brain Research, Amsterdam, The Netherlands (WJGH, JSP, MAH, DFS); Graduate School Neurosciences Amsterdam, Research Institute Neurosciences Free University, Department of Psychiatry, Valerius Clinic, Faculty of Medicine, Amsterdam, The Netherlands (WJGH); Regional Laboratory for Pathology Oost Nederland, Enschede, The Netherlands (RAIdV); and Medisch Spectrum Twente, Department of Neurology, Enschede, The Netherlands (ENHJ).

Address reprint requests to Witte J.G. Hoogendijk, MD, Valerius Clinic, Valeriusplein 9, 1075 BG Amsterdam, The Netherlands.

Received June 21, 1996; revised February 7, 1997; revised June 7, 1997; accepted June 13, 1997.

Table 1. Psychometrical and Clinical Data of Parkinson Patients during the Last 6 Months of Life

Patient number	DSM-III-R depression	Webster	MMSE	HDRS	Antiparkinsonian drugs used (dose in mg per day)	Other drugs used (dose in mg per day)
Depressed PD						
1. 93078	Major depression	7	26	27	No antiparkinsonian drugs used	Clozapine 150
2. 93067	Major depression	14	25	14	Bromocriptine 20, levodopa/carbidopa 375, selegiline 10	Piroxicam
3. 94047	Dysthymia	18	8	13	Levodopa/carbidopa 725, amantadine 200	Lormetazepam 2, digoxine
4. 94034	Major depression	26	13	24	Levodopa/carbidopa 625, selegiline 10	Baclofen
5. 94004	Major depression	10	17	21	Levodopa/carbidopa 750, amantadine 200, selegiline 10	No other drugs used
6. 93134	Dysthymia	13	13	16	Levodopa/benserazide 250, amantadine 200	Clozapine 50, lormetazepam 1
Mean $\pm$ SEM		14.7 $\pm$ 2.7	17.0 $\pm$ 2.9	19.2 $\pm$ 2.3		
Nondepressed PD						
7. 94132	—	19	9	10	Levodopa/benserazide 175, selegiline 10	Clozapine 100
8. 94062	—	22	12	7	Apomorphine 90, selegiline 10	Glibenclamide 5
9. 93029	—	20	16	11	Levodopa/benserazide 375, bromocriptine 15, selegiline 10	Digoxine, bumetanide
10. 93064	—	14	23	12	Levodopa/benserazide 750, bromocriptine 45, selegiline 10	Tiaprofenacid
11. 93109	—	10	11	7	Levodopa/benserazide 500, selegiline 10	Clozapine 75, temazepam 20
12. 92098	—	21	14	9	Apomorphine 70	Digoxine, beclometason
Mean $\pm$ SEM		17.7 $\pm$ 1.9	14.2 $\pm$ 2.0	9.3 $\pm$ 0.8		
M-W test		$p = .3$	$p = .4$	$p = .004$		

PD, Parkinson's disease; MMSE, Mini-Mental State Examination; HDRS, Hamilton Depression Rating Scale; SEM, standard error of the mean; M-W, Mann-Whitney *U* (two tailed).

diagnosed according to the DSM-III-R criteria (American Psychiatric Association 1987), and every 6 months the severity of the depressive symptoms was established with the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton 1967) by one of the authors (ENHJ) (Table 1).

In a consecutive and unselected series of 17 autopsies, brain tissue was obtained for morphometric analysis. Six PD patients were placed in the depressed group because they met the DSM-III-R criteria for major depression or dysthymia. All depressed patients had HDRS scores ≥ 13 . Depression preceded the onset of PD in 2 cases (nos. 2 and 5), recurred during the PD process in 3 cases (nos. 2, 4, and 5), and was present throughout the PD process in 1 case (no. 6). In none of the cases did depression only occur late in the disorder. From the remaining autopsy cases, 6 PD patients were selected who matched the depressed PD group as far as severity of cognitive impairment [Mini-Mental State Examination (MMSE); Folstein et al 1975], Parkinsonian symptoms (Webster scale; Webster 1968), and type and dose of antiparkinsonian drugs used (Table 1) were concerned. Clinical dementia was defined as an MMSE score < 20 in a patient who met the DSM-III-R criteria for dementia. In all demented patients, the cognitive decline started after the onset of PD and was most prominent late in the course of the PD process. The diagnoses of the depressed and nondepressed PD patients and of 6 controls were neuropathologically confirmed by one of

the authors (RAIdV). Semiquantitative analysis of cortical Lewy bodies was performed in the cingulate gyrus (de Vos et al 1995). The neuropathological diagnosis of Alzheimer's disease (AD) was based on the CERAD criteria (Mirra et al 1991). The three groups were matched according to sex, age, postmortem interval, brain weight, and fixation time. None of the patients died suddenly (e.g., suicide), and all were free of physical illnesses known to affect the HPA axis (Table 2).

The hypothalamus was serially sectioned at 6 μm . Sections were stained immunocytochemically for CRH at regular 300- μm intervals. After determining the volume of the PVN, numerical cell densities of CRH-expressing neurons per unit area were estimated in all sections by a discrete "unfolding" procedure (Raadsheer 1994b). The investigator (JSP) was blind to the diagnosis of the patient. The mean interrater measuring error of this method is only 8% (Purba et al 1993). Differences among the two and the three groups were tested two tailed using the Mann-Whitney *U* (M-W) and Kruskal-Wallis test (K-W), respectively, with $p < .05$ being statistically significant.

Results

The mean HDRS score of depressed PD patients (19.2 ± 2.3) was 10 points higher than that of nondepressed PD

Table 2. Morphometric and Clinical Data of Parkinson Patients and Controls

Patient number	Sex	Age (years)	Brain weight (g)	Postmortem delay (hours)	Fixation (days)	CRH neuron number (× 10 ³)	Other clinical diagnosis	DSM- III-R dementia	CERAD classification	CLB
Depressed PD										
1. 93078	F	68	1470	24	25	7.70	Psychosis	—	Normal	+
2. 93067	M	72	1464	24	35	4.77	Degenerative joint disease	—	Normal	+
3. 94047	F	73	1140	19	30	5.34	Decompensatio cordis	+	AD probable	+
4. 94034	M	77	1280	< 9	50	8.18	Spasticity	+	AD possible	++
5. 94004	F	78	1000	18	28	5.74	—	+	AD probable	++
6. 93134	M	79	1346	7	32	16.23	Anxiety	+	AD probable	+
Mean ± SEM	74.5 ± 1.7	1283 ± 76	16.8 ± 3.0	33.3 ± 3.6	7.99 ± 1.74					
Nondepressed PD										
7. 94132	M	61	1424	15	< 30	7.41	Psychosis	+	Normal	+
8. 94062	F	69	1422	24	28	6.31	Diabetes mellitus II	+	Normal	+
9. 93029	M	73	1055	11	< 30	11.34	Hypertension	+	AD probable	+
10. 93064	F	73	1165	24	24	8.18	Degenerative joint disease	—	Normal	+
11. 93109	F	78	1342	8	41	15.11	Psychosis	+	AD definite	++
12. 92098	M	86	1418	16	42	12.19	Decompensatio cordis, CARA	+	AD possible	+
Mean ± SEM		73.3 ± 3.4	1304 ± 64	16.3 ± 2.7	32.5 ± 3.0	10.09 ± 1.37				
Controls										
1. 93150	M	64	1417	48	< 30	8.20	Lung and pancreas carcinoma			
2. 9347	M	70	1454	5	28	5.06	Liver cirrhosis pneumonia			
3. 9249	M	71	1250	6	< 30	11.65	Sudden heart death			
4. 92048	F	72	1210	5	< 30	5.65	Decompensatio cordis			
5. 79472	F	72	1200	21	53	12.17	Endocarditis, frontal lobe infarct			
6. 94115	F	81	1290	7	29	4.33	Rectum carcinoma			
Mean ± SEM		71.7 ± 2.2	1303 ± 44	15.3 ± 7.0	33.3 ± 3.9	7.84 ± 1.39				
K-W test		<i>p</i> = .5	<i>p</i> = 1.0	<i>p</i> = .3	<i>p</i> = .9	<i>p</i> = .4				

PD, Parkinson's disease; AD, Alzheimer's disease; CLB, Cortical Lewy bodies (0 = none; + = less than 5; ++ = 5 or more in the cingulate gyrus); SEM, standard error of the mean; CARA, chronic aspecific respiratory ailment; K-W, Kruskal-Wallis (two tailed); CRH, corticotropin-releasing hormone.

patients (9.3 ± 0.8) ($p = .004$), whereas mean MMSE and Webster scores did not differ (Table 1).

All PD patients met the diagnostic criteria for definite PD (Mirra et al 1991), and all showed cortical Lewy bodies. One PD patient met the CERAD criteria for definite, 4 for probable, and 2 for possible AD. All nondemented and 2 demented patients were normal according to the CERAD classification (Table 2). Although our tissue sample of substantia nigra and locus coeruleus did not allow quantitative analysis, cell loss and Lewy bodies were evident in all PD patients.

The PVN volume occupied by the CRH-expressing

neurons in controls, depressed, and nondepressed PD patients was similar (4.27 ± 0.35 , 4.40 ± 0.50 , and $4.92 \pm 0.39 \text{ mm}^3$, respectively) ($p = .5$). The nuclear diameter of the CRH-expressing neurons in the three groups was also similar (7.94 ± 0.20 , 7.47 ± 0.22 , and $7.57 \pm 0.77 \text{ }\mu\text{m}$, respectively) ($p = .2$). The CRH-expressing neuron number in controls ($7.84 \pm 1.39 \times 10^3$) was not different from that of depressed ($7.99 \pm 1.74 \times 10^3$) or nondepressed ($10.09 \pm 1.37 \times 10^3$) PD patients ($p = .4$) (Table 2), or from that of the total PD group ($9.04 \pm 1.10 \times 10^3$) ($p = .5$). Even if the depressed PD group was restricted to major depression ($6.60 \pm 0.81 \times 10^3$), no difference was found

($p = .3$; K-W). Furthermore, the mean CRH-expressing neuron number of patients in whom depression preceded PD ($5.26 \pm 0.49 \times 10^3$) or recurred during the PD process ($6.23 \pm 1.01 \times 10^3$) was within the range found for the other PD patients. Irrespective of the presence of depression, the CRH-expressing neuron number in controls was not different from that of PD patients with ($9.76 \pm 1.37 \times 10^3$) or without ($6.88 \pm 1.07 \times 10^3$) clinical dementia ($p = .4$), or from that of PD patients with ($10.75 \pm 2.28 \times 10^3$) or without ($6.87 \pm 0.61 \times 10^3$) neuropathologically confirmed or probable AD ($p = .5$).

Discussion

The present study shows that depressed PD patients, nondepressed PD patients, the PD group as a whole (with or without coexisting AD), and controls do not differ with respect to CRH-expressing neuron number. This finding was independent of the type and moment of occurrence of the depression. The group of clinically nondemented patients comprised only 3 subjects, which is too small for a comparison with the demented patients. Since also the depressed PD group and the nondepressed PD group comprised only 6 subjects, our findings should be considered preliminary until they are replicated by another group. Overlapping symptomatology may theoretically result in false-negative findings, since both PD and dementia may mimic or obscure depressive symptoms, such as "depressed mood." These diagnostic pitfalls, however, seem inherent features of this kind of study, since the latest stage of the PD process, before the patient dies and comes to autopsy, is frequently accompanied by cognitive decline. Cognitive decline, in its turn, commonly obscures the depression, since demented patients may be less capable of expressing depression symptoms. In our study, however, the key symptom "depressed mood" and HDRS scores ≥ 13 were present in all subjects of the depressed group. Furthermore, PD pathology may have contributed to the cognitive decline in the 2 demented patients (nos. 7 and 8) without AD pathology, although Webster scale and cortical Lewy body scores were within the range of the other nondepressed patients. Finally, it seems extremely unlikely that a larger and more homogeneous group of more severely depressed PD patients would have given a different result, since both the subgroup of PD patients with major depression and the patients with high HDRS scores (> 20) did not even show a trend toward an increase of CRH-expressing neurons. The presumed inhibiting effect of levodopa on the HPA axis will not have influenced our results, since both groups of PD patients received a pharmacologically comparable type and dose of antiparkinsonian drugs and no antidepressants. It is of course possible that the CRH neurons in depressed PD

patients are activated, but that this is reflected, e.g., in the amount of CRH-mRNA (Raadsheer et al 1995) instead of in increased neuron number. The most probable explanation, however, is that depression in PD has a biological basis different from that of idiopathic depression. The fact, for instance, that the severity of vegetative symptoms increases with advancing PD, but mood and self-reproach do not (Huber et al 1990), and the finding that the correlation between the severity of motor impairment and depression in PD is poor (Mayeux et al 1984) may point toward a psychological, reactive contribution to the etiology of PD depression. Also, from a clinical point of view, depression in PD can be distinguished from other depressive disorders by greater anxiety and less self-punitive ideation (Cummings 1992). These observations and the findings of the present study [that activation of CRH neurons in the PVN, similar to what we observed in idiopathic depression (Raadsheer et al 1994a), does not occur in depression in PD] are in agreement with the hypothesis suggesting a different etiology for this type of depression.

This study was financially supported by The Netherlands Scientific Council (NWO; grant 900557007/716019) and the Deventer-Maas foundation.

We wish to thank W. Verweij for her secretarial help. Control brain tissue was obtained from the Netherlands Brain Bank (coordinator Dr. R. Ravid).

References

- American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed rev. Washington, DC: American Psychiatric Press.
- Brady LS, Gold PW, Herkenham M, Lynn AB, Whitfield HJ Jr (1992): The antidepressants fluoxetine, idazoxan and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: Therapeutic implications. *Brain Res* 572:117-125.
- Cummings JL (1992): Depression and Parkinson's disease. *Am J Psychiatry* 149:443-454.
- De Bellis MD, Gold PW, Geraciotti TD Jr, Listwak SJ, Kling MA (1993): Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am J Psychiatry* 150:656-657.
- de Vos RA, Jansen EN, Stam FC, Ravid R, Swaab DF (1995): "Lewy body disease": Clinico-pathological correlations in 18 consecutive cases of Parkinson's disease with and without dementia. *Clin Neurol Neurosurg* 97:13-22.
- de Vos RAI, Jansen ENH, Yilmazer D, Braak H, Braak E (1996): Pathological and clinical features of Parkinson's disease with and without dementia. In: Perry RH, McKeith IG, Perry EK, editors. *Dementia with Lewy Bodies*. Cambridge: Cambridge University Press, pp 255-267.

- Folstein MF, Folstein SE, McHugh PR (1975): "Mini-mental state": A practical method for grading the mental state of patients for the clinician. *J Psychiatr Res* 12:189-198.
- Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278-296.
- Holsboer F, Sprengler D, Heuser I (1992): The role of corticotropin-releasing hormone in the pathogenesis of Cushing's disease, anorexia nervosa, alcoholism, affective disorders and dementia. In: Swaab DF, Hofman MA, Mirmiran M, Ravid R, Van Leeuwen FW, editors. *The Human Hypothalamus in Health and Disease* (Progress in Brain Research 93). Amsterdam: Elsevier, pp 385-417.
- Huber SJ, Freidenberg DL, Paulson GW, Shuttleworth EC, Christy JC (1990): The pattern of depressive symptoms varies with progression of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 53:275-278.
- Mayeux R, Williams JB, Stern Y, Cote L (1984): Depression and Parkinson's disease. *Adv Neurol* 40:241-250.
- Mirra SS, Heyman A, McKeel D, et al (1991): The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 41:479-486.
- Purba JS, Hofman MA, Portegies P, Troost D, Swaab DF (1993): Decreased number of oxytocin neurons in the paraventricular nucleus of the human hypothalamus in AIDS. *Brain* 116:795-809.
- Raadsheer FC, Hoogendijk WJG, Stam FC, Tilders FJH, Swaab DF (1994a): Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology* 60:436-444.
- Raadsheer FC, Oorschot DE, Verwer RWH, Tilders FJH, Swaab DF (1994b): Age related increase in the total number of corticotropin-releasing hormone neurons in the human paraventricular nucleus in controls and Alzheimer's disease: Comparison of the disector with an unfolding method. *J Comp Neurol* 339:447-457.
- Raadsheer FC, Van Heerikhuizen JJ, Lucassen PJ, Hoogendijk WJG, Tilders FJH, Swaab DF (1995): Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am J Psychiatry* 152:1372-1376.
- Rabey JM, Scharf M, Oberman Z, Zohar M, Graff E (1990): Cortisol, ACTH, and beta-endorphin after dexamethasone administration in Parkinson's dementia. *Biol Psychiatry* 27:581-591.
- Webster DD (1968): Critical analysis of the disability in Parkinson's disease. *Mod Treat* 5:257-282.