SHORT REPORT

Apomorphine induced cognitive changes in Parkinson's disease

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Abstract

Auditory event related potentials (ERPs) and visual evoked potentials (VEPs) were recorded from eight patients with Parkinson's disease, before and after a single dose of apomorphine. To assess the treatment effects, the patients' motor state, Benton visual retention test (BVRT), and digit span tests were also examined. After apomorphine, although motor performance improved, the ERP latencies were delayed and the N2-P3 ERP amplitude was significantly diminished by comparison with pretreatment values. These data suggest that apomorphine induces, besides its motor effects in patients with Parkinson's disease, a slowing down of cognitive processing. Preferential stimulation of dopamine autoreceptors in mesocortical and mesolimbic systems may represent a neural mechanism for these effects. Also, the posttreatment BVRT rotation errors significantly increased, suggesting an apomorphine induced impairment of visuospatial perception.

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Dopaminergic deficiency is known as a fundamental mechanism of motor impairment in idiopathic Parkinson's disease and may also play an important part in parkinsonian cognitive deficits.¹ The benefit from levodopa treatment on cognition is usually less pronounced than that on motor symptoms. Some specific cognitive deficits may recover whereas others remain unimproved.² Several studies even found a degradation of cognitive functions in patients with Parkinson's disease under levodopa.³

The evaluation of cognitive deficits in Parkinson's disease is often complicated by the interference with motor disability. Electrophysiological methods of investigation, namely late "event related" auditory evoked potentials (ERPs) have thus been proposed as objective indicators of neural function in Parkinson's disease.⁴ Recently, ERPs were used to assess the effects of dopaminergic treatment in Parkinson's disease. After levodopa, the latency of the major cognitive component P3 (P300) was shortened, sug-

gesting a post-treatment improvement of cognitive processing,⁵ but another study, showed a delay of the P3 ERP after levodopa.⁶ Similarly, in healthy subjects, a single dose of levodopa provoked a prolongation of the P3 wave latency in comparison with the pretreatment values.⁷ Visual evoked potentials (VEPs) have also been assessed in patients with Parkinson's disease. The delay of the P100 wave, the major component of VEPs, have been proposed as a correlate of dopaminergic dysfunction in the retina and visual pathways.⁸

To improve our understanding of dopaminergic involvement in Parkinsonian cognitive deficits, we aimed to assess the behavioural effects of apomorphine, a potent direct agonist of D₁ and D₂ dopamine receptors with a rapid but short term effect. Transient sedation and sleepiness have often been seen in patients with Parkinson's disease after isolated doses of apomorphine but more profound analysis of this phenomenon and of its underlying mechanisms is not available.

Materials and methods

Eight patients with Parkinson's disease (five men and three women, mean age 59.4 (SD 8.3) years) were studied after giving informed consent. The mean duration of disease was 8.3 (6.4) years, with two patients classified as being in each of Hoehn and Yahr stages I, II, III, and IV. All of the patients were on dopaminergic medication with mean duration of 5.4 (4.8) years, and a mean levodopa dose of 422 (SD 294) mg. Only non-demented patients with mean mini mental status (MMS) score 28.6 (SD 2.2), with normal or corrected to normal vision, and with no signs or history of concurrent neurological or psychiatric diseases were included. Nine healthy volunteers (six men and three women, mean age 61.9 (SD 2.7) years) were taken as controls for ERP and VEP testing. A detailed interview, standard neurological examination, and MMS testing were done to include in the control group only subjects without previous history of neurological or psychiatric disorders, with normal neurological state, and MMS >28.

The ERPs were examined according to an auditory oddball paradigm requiring a mental count of rare target tones (2 kHz) randomly

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occurring ($p = 0.2$) in a sequence of frequent indifferent tones (1 kHz, $p = 0.8$), carried binaurally by headphones, and with an intensity of 75 dB. Evoked potentials were recorded from the vertex (Cz) with a reference to linked mastoids. Electrode impedance was maintained below 5 k Ω . The EEG data were amplified (filter bandpass 0.5–50 Hz), digitised, and averaged separately for target and indifferent tones by a Dantec E-4000. Trials with excessive eye movement were automatically rejected. At least two averages of 20 artifact free trials in response to target stimuli were obtained. The ERPs were analysed and the N1, P2, N2, and P3 waves were identified on the basis of sequence, polarity, and latency range, on the waveforms elicited by target stimuli. Latencies of ERPs were measured in ms from stimulus onset to wave peaks, amplitude values N1-P2 and N2-P3 were determined as the difference in μ V between the respective peaks.

The VEPs were examined monocularly, by successive stimulation of the right and left eyes. Pattern reversal vertical grating stimuli with square wave luminance profile, spatial frequency of 4 cpd, and temporal frequency of 1 Hz were generated on a TV screen placed 150 cm from the observer's eye and subtending 9° of his or her visual field. The mean luminance of the screen was 619 cd/m², the contrast was 95%. The VEPs were recorded from Oz referenced to Fz. Filter bandpass was set at 1 and 100 Hz and analysis time was 400 ms. At least two averages of 200 artifact free trials were performed to ensure reproducibility. The latencies of N70, P100, and N140 VEP components were measured in ms, from stimulus onset (pattern reversal) to peak; VEP amplitude was determined by measuring the difference in μ V between the peaks of N70 and P100.

A short battery of neuropsychological tests included the Benton visual retention test, administration A (BVRT), and forward and backward digit span tests (DS). On the BVRT examination, after a 10 second exposure to each of 10 cards of one or three figure design, an immediate recall by drawing was demanded. To minimise practice effects, two

equivalent forms of the BVRT (C and D) were made before and after apomorphine. The numbers of correct reproductions and of errors were recorded (more than one error per card was counted if different errors were combined). The DS tests required an immediate recall of digit series (from 1 to 9) of increasing length. The forward and backward DS represent the largest numbers of digits correctly repeated in a given order.

At least 48 hours before tests, 20 mg domperidone given three times daily. All medication except for domperidone was withdrawn 12–14 hours before the testing. The patients were tested twice during the same experimental session, before and after apomorphine (a dose of apomorphine hydrochloride in water corresponding to 0.05 mg of apomorphine/kg of weight, injected subcutaneously). Both parts of the testing were identical in arrangement and duration (40–45 minutes); the second part started 15 minutes after apomorphine. Examination of ERPs and VEPs and neuropsychological testing were conducted as described. The patients' motor status was evaluated according to the Columbia University rating scale (CURS) in which the maximum disability score = 100.

Results

After apomorphine, motor performance in eight patients was greatly improved in comparison with the pretreatment condition. The average CURS score decreased from 32.5 (SD 24.6) before apomorphine to 14.5 (9.7) after apomorphine ($p < 0.05$ on paired Wilcoxon test). No further changes exceeding 10% of post-treatment CURS values were noted until the end of the examination.

All patients and control subjects were able to perform the ERP task and the target count errors did not exceed ± 2 . The electrophysiological data obtained from patients with Parkinson's disease and from controls were compared by Mann-Whitney U tests. The indices of the ERP recorded in patients with Parkinson's disease before apomorphine did

Table 1 Event related potentials and visual evoked potentials in eight patients with Parkinson's disease

Variable	Controls (n = 9)	PD patients (n = 8)	
		Before APO (mean (SD))	After APO (mean (SD))
ERP:			
N1 latency (ms)	93.8 (9.1)	96.5 (27.1)	106.8 (12.9)*
P2 latency (ms)	175.1 (12.6)	174.3 (20.5)	190.3 (19.4)
N2 latency (ms)	234.0 (17.3)	236.3 (29.2)	271.3 (39.3)**††
P3 latency (ms)	343.8 (31.2)	347.8 (42.1)	381.8 (33.9)
N1-P2 amplitude (μV)	11.1 (3.2)	13.1 (5.9)	14.5 (5.6)
N2-P3 amplitude (μV)	13.1 (4.6)	15.9 (12.0)	9.4 (7.0)†
VEP:			
N70 latency (ms)	85.9 (7.1)	85.6 (8.9)	83.9 (8.0)
P100 latency (ms)	115.9 (8.5)	113.1 (9.7)	116.4 (11.6)
N140 latency (ms)	153.7 (8.9)	150.9 (24.7)	158.4 (24.8)
N70-P100 amplitude (μV)	6.2 (2.1)	4.7 (2.8)*	3.9 (2.5)**

* $p \leq 0.05$; ** $p \leq 0.01$; patients with Parkinson's disease v controls (Mann-Whitney U test)
† $p \leq 0.05$; †† $p \leq 0.01$; patients with Parkinson's disease before v after apomorphine (paired Wilcoxon test).

Figure 1 Event related potentials recorded at Cz from a control subject (trace 1) and from a patient with Parkinson's disease before (trace 2) and after (trace 3) a single dose of apomorphine. Each trace represents the average of 40 responses to the target tone. Note the relative delays of the N2 and P3 waves after apomorphine compared with the control and with the pretreatment waveform.

Figure 2 Visual evoked potentials recorded from Oz in a control subject (trace 1) and in a patient with Parkinson's disease before (trace 2) and after (trace 3) a single dose of apomorphine. Each tracing represents an average of 400 responses elicited by right and left eye stimulation. Note the post-treatment modifications of waveform shape with slightly delayed P100 and N140 latencies in comparison with the potentials recorded before apomorphine.

not differ from control values but the post-treatment N1 and N2 ERP latencies were significantly delayed in comparison with control data.

Latencies in ERPs generally increased after apomorphine compared with the pretreatment values. This increase was significant for the N2 ERP latency and just under the significance thresholds for the P2 and P3 latencies, as assessed by Wilcoxon paired tests. Also, the N2-P3 ERP interpeak amplitude was significantly diminished after apomorphine compared with the pre-treatment results (table 1, fig 1).

The latencies of the VEP recorded in patients with Parkinson's disease did not differ from control data. The N70-P100 VEP amplitudes were significantly lower in patients with Parkinson's disease than in controls, both before and after apomorphine. Slight and non-significant delays of the P100 and N140 wave latencies were found after apomorphine compared with the pretreatment values (table 1, fig 2).

The pretreatment numbers of correct BVRT reproductions were within normal limits and remained unchanged after apomorphine. Total BVRT error scores were somewhat higher after apomorphine than before. This was mainly due to the significant

rise of figure rotation errors and, to a lesser extent, of omissions. Scores for DS were within normal limits and did not significantly change after apomorphine (table 2).

Spearman rank correlations calculated between electrophysiological and neuropsychological data (both before and after apomorphine) and the age of the patients, duration of Parkinson's disease, duration and dose of levodopa treatment, MMS, and CURS scores, were not significant.

Discussion

In eight non-demented patients with Parkinson's disease, motor disability as assessed by CURS was improved after apomorphine, whereas cognitive performance as indexed by ERP was worse after than before apomorphine.

These results are similar to previous findings of improved motor performance and delayed ERP after levodopa in patients with Parkinson's disease.⁶ The delays in the ERP components seem to represent a slowing down of neural events underlying perception, discrimination, and categorisation of stimuli,⁹ the post-treatment reduction of the P3 ERP amplitude corresponding to a decrease of the stimulus information amounts processed.¹⁰ Also, on BVRT which provides measures of visuospatial cognitive functions, our patients had significant post-treatment increases in rotation errors, indicating an apomorphine-induced impairment of visual perception.

The contrasting effects of dopaminergic treatment, improving overall motor performance but impairing some aspects of cognitive processing, might be interpreted in the light of several earlier studies. After apomorphine treatment in low doses, laboratory animals showed decreased motor activity and yawning behaviour, whereas higher doses produced hypermobility and stereotypy.¹¹ These biphasic behavioural responses were attributed to a selective drug action at presynaptic and postsynaptic dopamine receptors.¹² The presynaptic dopamine "autoreceptors" were shown to be more sensitive to the effects elicited by dopamine agonists than the postsynaptic receptors in the striatum. Low doses of dopamine agonists thus produce an inhibition of dopaminergic activity, and larger doses act to stimulate postsynaptic receptors directly eliciting the expected response. Furthermore, presynaptic dopamine receptors in the mesocortical system seemed to be more sensitive to dopamine agonists than the autoreceptors on the terminals of the nigrostriatal neurons.¹² Preferential stimulation of dopamine autoreceptors in the mesocortico-limbic system might, therefore, explain the post-treatment ERP delays in patients with Parkinson's disease. Denervation supersensitivity of postsynaptic dopamine receptors in the striatum may account for the parallel improvement of motor performances induced by apomorphine. Of course, more complex interactions within distinct subpopulations of postsynaptic dopamine receptors or within non-

Table 2 Neuropsychological tests in eight patients with Parkinson's disease

Variable	Before apomorphine (mean (SD))	After apomorphine (mean (SD))
Benton visual retention test:		
Correct reproductions	5.0 (2.1)	4.8 (2.0)
Total number of errors	7.0 (2.7)	8.5 (4.9)
Rotation errors	1.1 (0.8)	2.5 (0.9)†
Omissions	0.5 (0.8)	1.5 (1.8)
Distortions	2.5 (2.0)	1.6 (1.9)
Misplacements	1.3 (1.0)	1.9 (1.6)
Size errors	1.1 (1.7)	0.9 (0.8)
Digit span:		
Forward	5.9 (0.8)	6.3 (1.0)
Backward	3.5 (0.9)	4.1 (1.8)

p ≤ 0.05; patients with Parkinson's disease before v after apomorphine (paired Wilcoxon test).

dopaminergic neurotransmitter systems may occur.

On the other hand, taking into account the fixed order of testing in the same session, the findings might be interpreted as non-specific effects of apomorphine on arousal. Such an interpretation, however, seems unlikely, given that the DS test performances remained unchanged with the treatment, indicating a preserved level of attention all through the testing.

Finally, the pretreatment latencies of the ERP and VEP recorded in our non-demented patients with Parkinson's disease were not different from the control data. For ERP, this is in accordance with the fact that definite latency delays have generally been shown in demented but not in non-demented patients with Parkinson's disease, reflecting probably cognitive slowing down associated with dementia.^{4,13} On VEP testing, normal latencies and reduced amplitudes were found in the present study similar to, for example, the non-demented patients (mean MMS = 28.2) of Hansch *et al.*¹⁴ Several other studies, however, showed delayed VEP in Parkinson's disease, the P100 VEP being more delayed "off" than "on" levodopa.⁸ Without elaborating on dopaminergic involvement of the visual system in Parkinson's disease, on the basis of this discussion, perhaps the definite VEP delays might also be related to the presence of dementia in patients with Parkinson's disease, as ERPs are. In most previous VEP studies, the patients' mental state was not, unfortunately, specified. Interestingly, a significant prolongation of VEP latencies was recently reported in demented as distinct from non-demented patients with Parkinson's disease.¹⁵

In conclusion, the present results show that apomorphine modifies some aspects of cognitive functioning in non-demented parkinsonian patients. Preferential stimulation of the presynaptic dopamine receptors in the mesocortical and mesolimbic system may at least partly explain these findings. Further studies should be undertaken in both demented and non-demented patients with Parkinson's

disease, employing more specific test paradigms focused on isolated cognitive deficits, to shed light on complex subcortical interactions supposedly occurring under dopaminergic treatment in Parkinson's disease.

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