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BLOOD PRESSURE RESPONSES TO NORADRENALINE AND DOPAMINE INFUSIONS IN PARKINSON'S DISEASE AND THE SHY-DRAGER SYNDROME

C.S. WILCOX† & M.J. AMINOFF*

Departments of Pharmacology & Therapeutics and Neurological Studies, The Middlesex Hospital Medical School, London W1P 7PN

1 Studies of pulse rate and blood pressure responses to graded intravenous infusions of noradrenaline and dopamine were performed on five patients with Parkinson's disease, five with the Shy-Drager syndrome and seven healthy subjects. Cardiovascular reflex responses to standing and to the Valsalva manoeuvre were found to be preserved in all patients with Parkinson's disease but to be grossly defective or absent in all with the Shy-Drager syndrome.

2 Each subject received separate intravenous infusions of L-noradrenaline and dopamine, delivered at increasing rates, until a 30% rise in systolic blood pressure was achieved.

3 Heart rate decreased during pressor responses to noradrenaline in control subjects and patients with Parkinson's disease, but increased in those with the Shy-Drager syndrome. Heart rate increased during pressor responses to dopamine in all subjects.

4 Compared to control subjects supersensitivity to noradrenaline was observed both in patients with Parkinson's disease and, to a greater extent, in those with the Shy-Drager syndrome. Subsensitivity to dopamine was observed in patients with Parkinson's disease, but supersensitivity in those with the Shy-Drager syndrome.

Introduction

Orthostatic hypotension is a well recognised side effect of treatment for Parkinson's disease with levodopa (Calne, Brennan, Spiers & Stern, 1970). However, in patients with the Shy-Drager syndrome (a motor system degenerative disorder in which Parkinsonism and autonomic failure are conspicuous features) a rise in both recumbent and erect blood pressures may occur (Aminoff, Wilcox, Woakes & Kremer, 1973), while in normal subjects levodopa has no consistent effect on blood pressure (Ansel & Markham, 1970).

Levodopa itself is probably inert (Hornykiewicz, 1966). Its activity follows conversion in the body to its major metabolites, dopamine and noradrenaline. The abnormal blood pressure responses to levodopa observed in patients with Parkinson's disease and the Shy-Drager syndrome could therefore reflect abnormalities in their cardiovascular responses to dopamine and noradrenaline. This hypothesis was tested in the present study by contrasting the blood pressure responses to these catecholamines of patients with these disorders to that of a control group of healthy subjects. Catecholamines given by the intravenous route are largely excluded from the brain, although some may penetrate in significant quantities to certain regions such as the hypothalamus (Bertler, Falck, Owman & Rosengrenn, 1966). Thus our experiments have mainly tested the extracerebral mechanisms or those excited extracerebrally.

Investigations performed on patients with the Shy-Drager syndrome reveal pathological and functional evidence of central and/or peripheral lesions in the sympathetic nervous system (Aminoff & Wilcox, 1971). For ease of interpretation, we selected for study those patients with the Shy-Drager syndrome who had functional evidence of a lesion of post-ganglionic peripheral sympathetic neurones. Patients with Parkinson's disease were selected only in that they were in hospital for consideration of levodopa therapy.

† Present address: Medical Unit, St Mary's Hospital, London W2 1NY.

* Present address: The National Hospital for Nervous Diseases, Maida Vale, London W9 1TL.

Methods

Subjects

All patients were in hospital prior to starting levodopa therapy for the Parkinsonism from which they suffered. They were all ambulatory and were receiving daily physio- and occupational therapy. All had normal values for plasma urea and electrolytes, and normal electrocardiograms. Two patients (one with Parkinson's disease and one with the Shy-Drager syndrome) were receiving orphenadrine hydrochloride (300 mg daily) and the remaining eight were receiving benzhexol (4 – 8 mg daily). None was receiving levodopa, amantadine or any drugs known to affect catecholamine storage or metabolism. The patients were divided into two groups (Table 1).

The first group consisted of five patients with Parkinson's disease. They were selected only in that they were in hospital for consideration of levodopa therapy. Their cardiovascular reflex responses to change in posture and to the Valsalva manoeuvre were preserved. Intravenous lobeline hydrochloride induced coughing and hyperpnoea, demonstrating the integrity of afferent chemoreceptor pathways. Intradermal injections of acetylcholine induced a spreading piloerection and sweating response, indicating the integrity of post-ganglionic sympathetic neurones. References to the interpretation of these tests of autonomic function are cited by Aminoff & Wilcox (1971).

The second group consisted of five patients with the Shy-Drager syndrome. They had conspicuous Parkinsonian signs in association with a pyramidal and lower motor neurone deficit, and a gross derangement of cardiovascular reflex responses. There was severe orthostatic hypotension on standing or on passive tilting to 70°, and an absent or grossly abnormal reflex response to the Valsalva manoeuvre. They responded normally to intravenous lobeline hydrochloride by coughing and hyperpnoea. Intradermal injection of acetylcholine produced a prominent local response of piloerection and sweating at the injection site, but the spreading component of the response was absent. Responses of this kind are seen in subjects after post-ganglionic sympathectomy (Janowitz & Grossman, 1950; Barany & Cooper, 1956). A patient with the Shy-Drager syndrome whose spreading response to intradermal acetylcholine was preserved was excluded from this study.

The control group consisted of seven subjects. Six of these were healthy, but the seventh (Ro) had been receiving absolute bed-rest in hospital for seven days prior to the tests, because of acute sciatica. Five of the control subjects received

Table 1 Clinical data

	Control subjects							*Parkinson's disease*						*Shy-Drager syndrome*				
	Ro	A	M	W	K	J	Ri	K	G	R	B	Bl	M	B	Sp	Sm	P
Age (years)	58	32	31	30	33	28	59	65	55	48	59	61	48	57	48	68	63
Sex	M	M	M	M	M	F	M	M	F	M	M	F	M	F	F	F	M
Weight (kg)	78	64	68	76	79	51	68	105	51	71	66	69	70	50	50	61	77
Recumbent systolic BP (mmHg)	115	135	110	130	110	110	120	140	120	125	140	120	120	155	135	145	130
Neurological signs:																	
Extrapyramidal	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+
Other motor systems	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+

benzhexol (6 mg daily for 2 days before, and 2 mg on the morning of the tests).

Informed consent was obtained from all participants. They were told that they would receive intravenous infusions of two substances which would cause a small rise in their blood pressure. Permission to perform the study was obtained from the Clinical Investigations Panel of the Middlesex Hospital.

Experimental procedure

All subjects were recumbent in bed throughout the tests. A forearm vein was cannulated between 09.00 h and 10.00 h, and 1 h allowed before any catecholamines were infused. During this time, and also in the interval between catecholamine infusions, 0.28 M dextrose solutions were infused at a rate of about 1 ml min^{-1} to maintain the patency of the intravenous cannula. Solutions of catecholamines were infused through the cannula from a motor-driven syringe (Palmer) at a constant rate of 16 ml min^{-1}. Blood pressure was recorded by one observer with a sphygmomanometer at the beginning and end of each period of catecholamine infusion. A second observer recorded the radial pulse rate at these times. One catecholamine (either noradrenaline or dopamine) was first infused for 4 min; there followed a 4 min period during which the subject received only 0.28 M dextrose solution before the same catecholamine, but in higher concentration, was again infused for a 4 min period. This process was repeated until a 30% rise in systolic blood pressure ('maximal' pressor response) was obtained. Ninety minutes after the 'maximal' pressure response was obtained with the first catecholamine, the same infusion process was repeated, using the other catecholamine. The order in which the catecholamines were infused was randomised within the three groups of subjects. An infusion period of 4 min was chosen because pilot studies on one subject had shown that a longer period of infusion did not produce a greater rise in blood pressure.

Solutions of L-noradrenaline tartrate (Levophed–Winthrop) were freshly made up in 0.154 M saline on the day of the tests to yield concentrations of 31, 62, 124, 186, 310, 465, 620, 775 and 930 μg base $litre^{-1}$. Solutions of dopamine hydrochloride (Ciba) were made up in 0.154 M saline and passed through millipore filters on the day before the tests were performed. They were kept at 4° C overnight. The initial concentration used was 12.5 mg base $litre^{-1}$, and subsequent increments were all of 12.5 mg base $litre^{-1}$.

The data obtained in each of the three groups of subjects were analysed for a relationship between the percentage increase in systolic blood pressure and the logarithm of the rate of infused catecholamine (corrected for body weight). In this analysis the results of all infusions yielding a systolic pressor response of greater than 5 mmHg were included. The results for subjects within individual groups were combined. The increase in pressure was calculated as the difference between the systolic value measured before each catecholamine infusion period and the systolic value measured at the end of the subsequent infusion. An approximately linear relationship was observed for each group. A computer was used to obtain regression lines, using a least square fit, and correlation coefficients for the equation:

$$y = m(\log_e x) + c$$

where y = % increase in systolic blood pressure and x = rate of catecholamine infusion/kg body weight. From the data the 5% confidence limit for m and c were obtained. Threshold rates of catecholamine infusion were expressed as the intercepts of the regression lines on the x axis. Statistical methods are those described in Armitage (1973).

Results

No adverse reactions were encountered during the infusions, and the only objective symptom produced was an awareness of increased heart rate during the dopamine infusions.

Noradrenaline infusions

Typical responses of a control subject, a patient with Parkinson's disease and a patient with the Shy-Drager syndrome to noradrenaline infusions are shown in Figure 1. The pressor response to noradrenaline can be seen to include a rise in both systolic and diastolic blood pressures. By 4 min after the end of each noradrenaline infusion, blood pressure readings had returned to values equal or close to pre-infusion ones. It can be seen also that both patients required less noradrenaline than the control subject to develop a pressor response. All of the control subjects and patients with Parkinson's disease developed a bradycardia during the noradrenaline-induced 'maximal' pressor response, whereas all of the Shy-Drager subjects had a tachycardia (Table 2).

Figure 3 relates the percent increase in systolic blood pressure to the logarithm of the rate of noradrenaline infusion per unit of body weight for each of the three groups of subjects. Compared to control subjects, both the patients with Parkinson's disease and those with the Shy-Drager

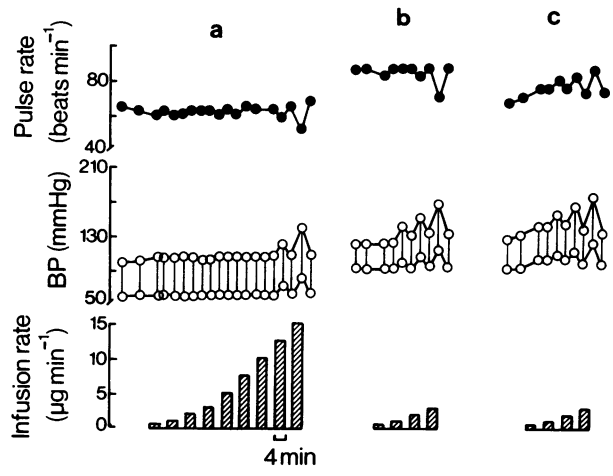

Figure 1 Blood pressure and pulse rate responses to noradrenaline infusions in a control subject (a, age 59 years; weight 68 kg), a patient with Parkinson's disease (b; age 48 years; weight 71 kg) and a patient with the Shy-Drager syndrome (c; age 63 years; weight 77 kg).

syndrome required a lesser rate of noradrenaline infusion to raise the systolic blood pressure. An analysis of the data shown in Figure 3 is presented in Table 3. The variation of response within each group was low ($r > 0.95$). In both groups of patients, the slope (m) of the regression line of percentage increment in blood pressure on the logarithm of the rate of noradrenaline infusion was within the 5% confidence limit of the normal subjects, but the value for c was outside these limits. The supersensitive pressor responses in both groups of patients can therefore be expressed by parallel shifts of log dose-response curves to the left. Compared to control subjects, the rate of infusion calculated to raise the systolic blood pressure by 30% was reduced to an average of 28% in patients with Parkinson's disease and to an average of 16% in patients with the Shy-Drager syndrome.

One healthy subject (Ri) was studied before and 2 days after receiving benzhexol (6 mg daily). This dose of anti-cholinergic drug did not alter pre-infusion values of recumbent pulse rate or blood pressure, nor did it alter the blood pressure responses to noradrenaline infusions.

Dopamine infusions

Typical responses of a control subject, a patient with Parkinson's disease and a patient with the Shy-Drager syndrome to dopamine infusions are shown in Figure 2. Compared to the control subject, considerably more dopamine was required to induce the pressor response in the patient with

Table 2 Mean pulse rate (range in brackets) before and during catecholamine infusions

	Pulse rate		
	Before (beats min⁻¹)	*Noradrenaline (% change)*	*Dopamine (% change)*
Control subjects	65 (52, 75)	−15 (−2, −22)	+12 (+5, +22)
Parkinson's disease	72 (58, 84)	−13 (−3, −20)	+18 (+6, +32)
Shy-Drager syndrome	69 (52, 80)	+14 (+8, +28)	+18 (+2, +30)

The pulse rate measurements were made at the time of the 'maximal' pressor response.

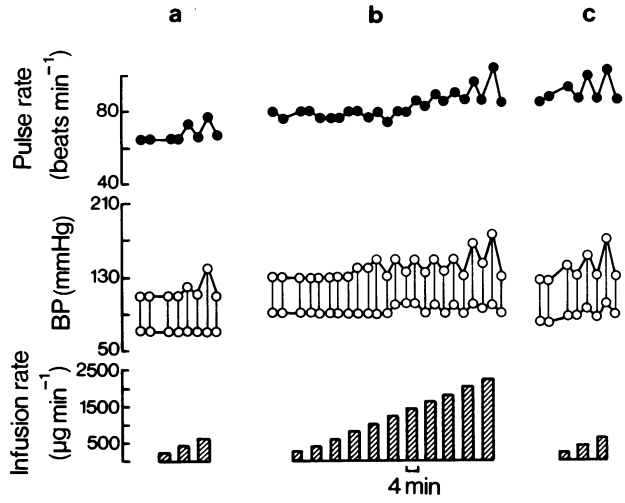

Figure 2 Blood pressure and pulse rate response to dopamine infusions in the same subjects as shown in Figure 1.

Parkinson's disease, but not in the patient with the Shy-Drager syndrome. Pressor responses to dopamine involved a rise in systolic blood pressure with little or no rise in diastolic pressure; consequently pulse pressure increased. The pulse rate increased in all subjects tested during the dopamine infusion and the degree of tachycardia observed at the height of the 'maximal' pressor response was comparable in the three groups of subjects (Table 2).

The group data are shown in Figure 3. The Shy-Drager patients required rather less dopamine to raise the blood pressure than did the control subjects. The variation in response within these two groups was low ($r > 0.94$). The value for c amongst the Shy-Drager patients falls outside the 5% confidence limit of the normal subjects (Table 3) and there is also a significant reduction in slope (m). In these patients the calculated dose required to raise the systolic blood pressure by 30% was

Table 3 Data for calculated regression lines relating increase in BP to rate of catecholamine infusion

	n	r	*Noradrenaline* *m*	(*ng kg⁻¹ min⁻¹*) *c*	*Calculated threshold dose*	*Calculated dose to raise systolic BP by 30%*
Control subjects	15	+0.97	31	−143	91	251
			(27 to 36)	(−118 to −167)		
Parkinson's disease	11	+0.98	34	−115	29	70
Shy-Drager syndrome	7	+0.96	35	−106	20	41
			Dopamine	(*μg kg⁻¹ min⁻¹*)		
Control subjects	12	+0.98	37	−60	5.1	11.3
			(32 to 43)	(−49 to −72)		
Parkinson's disease	14	+0.80	19	−36	6.3	29.6
Shy-Drager syndrome	7	+0.94	25	−13	1.7	5.5

Equations for the regression lines drawn in Figure 3 have the form:
% rise in systolic blood pressure = ($\log_e$ rate of catecholamine infusion/ kg body weight) + c
n number of observations; *r* correlation coefficient; calculated doses are those obtained from the regression lines.
5% confidence limits for m and c are shown in brackets.

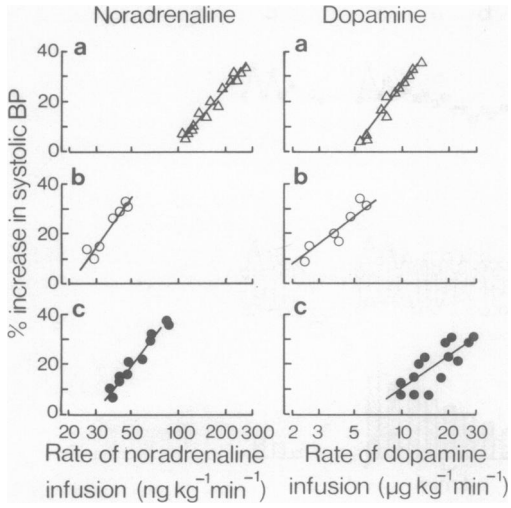

Figure 3 The relationship between the percentage increase in systolic blood pressure and the rate of noradrenaline or dopamine infusion (log scale and expressed per unit of body weight). The results of all infusions yielding a systolic pressor response greater than 5 mmHg have been included; these results have been combined for all control subjects (a), patients with the Shy-Drager syndrome (b) and patients with Parkinson's disease (c). The regression constants for the lines drawn are shown in Table 3.

reduced to an average of 49% of that required in healthy subjects.

In contrast to their responses to noradrenaline, patients with Parkinson's disease were subsensitive to the pressor effect of dopamine. There was a greater variation within the group in their response ($r > 0.80$). Their subsensitivity was due to a considerable reduction in the slope of the dose-response curve (Table 3). Accordingly, although their calculated threshold dose was similar to that of control subjects, the rate of dopamine infusion calculated to produce a 30% rise in systolic blood pressure was 260% of that for control subjects.

Table 1 shows that the three groups of subjects were well matched for body weight, but that the mean pre-infusion blood pressure and the mean age of the control subjects were below that of the experimental groups. However, the pressor sensitivity of the two oldest control subjects (aged 58 and 59 years) to the catecholamine infusions (one of which is illustrated in Figures 1 and 2) was similar to that seen in the remaining younger control subjects.

The pressor sensitivity of the control subject (Ro) who had been confined to bed for 10 days before testing was similar to that observed in the ambulant control subjects.

Discussion

The rise in blood pressure during a slow intravenous noradrenaline infusion in a normal subject is due to raised peripheral resistance since, with reflex bradycardia, the cardiac output usually falls slightly (Barcroft & Swan, 1953). Both our control subjects and patients with Parkinson's disease exhibited bradycardia during the pressor responses; conversely our Shy-Drager patients (in whom cardiovascular reflexes were impaired or absent) developed a tachycardia. These patients with the Shy-Drager syndrome may well have had an increase in cardiac output during noradrenaline infusion and this would have contributed to the supersensitive blood pressure responses observed.

On the other hand, the rise in blood pressure during a slow intravenous dopamine infusion in normal subjects is largely due to increased cardiac output, and peripheral resistance changes little (Horwitz, Fox & Goldberg, 1962). Our observations that dopamine, unlike noradrenaline, increased the pulse pressure (Figures 1 and 2) would be quite consistent with this conclusion.

Dopamine increased heart rate although there was considerable variability between subjects of each group. Dopamine has been shown to stimulate adrenoceptors by both direct and indirect means (Goldberg, 1972). Spiers & Calne (1969) observed that the mydriatic response to dopamine eye drops was abolished by prior application of guanethidine, suggesting that this response was mediated indirectly through noradrenaline release. However, dopamine infusions in man, while increasing dopamine excretion twenty-five-fold, do not alter noradrenaline excretion (Atuk, Ayers & Westfall, 1968). Furthermore, we observed a supersensitive response to dopamine in patients with the Shy-Drager syndrome who had functional evidence of a lesion of post-ganglionic sympathetic neurones. In these subjects peripheral stores of noradrenaline were presumably very low and thus a subsensitive rather than a supersensitive response to an indirectly acting catecholamine would be anticipated.

Cannon & Rosenblueth (1949) observed an increase in sensitivity to catecholamines after post-ganglionic sympathectomy. Trendelenburg (1963) has proposed that reduced catecholamine clearance from the vicinity of the receptor contributes to this 'denervation supersensitivity'. Normally, administered noradrenaline is rapidly

taken up into sympathetic nerve terminals. The affinity of dopamine for this amine uptake process is also high (Iversen, 1967). Therefore, according to Trendelenburg's hypothesis, denervation should lead to enhanced responses to both dopamine and noradrenaline. Results from *in vitro* animal experiments using cat's iris (Marley, 1962) and rat's vas deferens (Birmingham, Paterson & Wojcicki, 1970) have confirmed this prediction but show that denervation increases sensitivity to dopamine rather less than to noradrenaline.

All patients with the Shy-Drager syndrome included in this study had functional evidence of post-ganglionic sympathetic denervation and this accords with the reported occurrence of degenerative changes in the sympathetic ganglia of patients dying from this disease (Shy & Drager, 1960). The markedly enhanced blood pressure response to infused noradrenaline that we found in these patients confirms earlier reports (Chokroverty, Barron, Katz, del Greco & Sharp, 1969). It may be attributed to a reduced rate of noradrenaline clearance because of a failure of neuronal uptake. The lesser degree of supersensitivity to dopamine observed in these patients is consistent with the animal experiments quoted above.

We found that patients with Parkinson's disease were also supersensitive to infused noradrenaline, although to a lesser degree than those with the Shy-Drager syndrome. This confirms the previous report of Birkmayer & Hornykiewicz (1964) who found pressor supersensitivity to subcutaneous injections of noradrenaline in 10 patients with Parkinson's disease. In contrast, Reid, Calne, George & Vakil (1972) injected an intravenous bolus of noradrenaline into patients with Parkinson's disease and found no evidence of altered pressor sensitivity. This method of administration produces a much wider scatter of results than does steady intravenous infusion, and this may have obscured an abnormal response. Moreover, the magnitude of the transient responses obtained by the bolus injection technique, unlike the steady responses produced by sustained infusion, must depend upon the rate of presentation of the drug to receptors. It will thus be influenced by such secondary factors as the rate of flow of blood in, and capacity of, the venous conduit used for the infusion, and the resting cardiac output.

The cause of the supersensitivity to noradrenaline in patients with Parkinson's disease is not clear. It is unlikely to be due to sympathetic denervation, since these patients have normal cardiovascular reflex responses to the Valsalva manoeuvre and to orthostasis. Furthermore, spreading piloerection and sweating occurred around the site of an intradermal injection of acetylcholine in these subjects, indicating the functional integrity of post-ganglionic sympathetic neurones (Barany & Cooper, 1956). Moreover, patients with Parkinson's disease were subsensitive to dopamine infusion, whereas those with the Shy-Drager syndrome, who had evidence of gross sympathetic denervation, were supersensitive. Thus, the pattern of pressor sensitivity to infused catecholamines was quite different in these two diseases. It has recently been shown that the pressor response to noradrenaline is enhanced in human subjects with chronic sympathetic decentralization (Christensen, Frankel, Mathias & Spalding, 1975). Tests of autonomic function performed on patients with Parkinson's disease are consistent with a central lesion which diminishes the tone of the sympathetic nervous system but spares major cardiovascular reflex pathways. Such a lesion might also explain the enhanced pressor sensitivity to noradrenaline observed in patients with this disease, as previously suggested by us (Aminoff & Wilcox, 1971).

Certain of our findings might be accounted for by a generalised abnormality of catecholamine metabolism, as has been reported by Barbeau (1969) to occur in Parkinson's disease. Thus, Barbeau & Trombitas (1967) found a 9 to 20-fold increase in the rate at which administered dopamine is converted to orthomethylated derivatives. An increase in metabolism of infused dopamine in our patients with Parkinson's disease would increase its rate of clearance from the circulation and therefore reduce its concentration at receptor sites. This might explain the pressor subsensitivity to dopamine.

The mechanisms whereby levodopa affects blood pressure are complicated and are believed to include both a depressor action mediated at cerebral sites and a pressor action mediated at extracerebral ones (Henning & Rubenson, 1970). Unlike levodopa, infused noradrenaline and dopamine do not cross the blood-brain barrier in appreciable quantities (Bertler *et al.*, 1966). Therefore, the pressor responses that we studied must presumably follow an action largely initiated at extracerebral sites. The supersensitivity to noradrenaline and dopamine in patients with the Shy-Drager syndrome will enhance that component of the response to levodopa that is due to extracerebral noradrenaline and dopamine generation and thereby contribute to the rise in blood pressure seen during levodopa therapy in such patients (Aminoff, Wilcox, Woakes & Kremer, 1973). But whether the contrasting changes in pressor sensitivity to noradrenaline and dopamine that we observed in patients with Parkinson's disease contribute to their response to levodopa is less clear and requires further study.

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