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Postprandial hypotension in de novo Parkinson's disease: A comparison with orthostatic hypotension

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ABSTRACT

Background: Postprandial hypotension (PPH) is often associated with Parkinson's disease (PD). However, its mechanism remains to be fully defined. We investigated the mechanism of PPH and compared it with that of orthostatic hypotension (OH).

Methods: The subjects were 37 patients with de novo PD and 10 healthy age-matched controls. We studied changes in blood pressure (BP), plasma norepinephrine concentrations (NE), plasma insulin, plasma glucose concentrations during a 75-g oral glucose tolerance test (75-g OGTT). Changes in BP and NE were also examined with head-up tilt-table testing (HUT).

Results: The maximum fall in systolic BP (SBP) on 75-g OGTT (ΔSBP_{PPH}) significantly correlated with that on HUT ($r = 0.359$, $p < 0.05$). On 75-g OGTT, ΔSBP_{PPH} significantly correlated with SBP after 20 min of rest in the supine position ($r = 0.394$, $p < 0.01$) and the time in which SBP reached its lowest ($r = 0.436$, $p < 0.01$). ΔSBP_{PPH} did not correlate with NE, plasma insulin and glucose concentrations after glucose loading, but significantly negatively correlated with NE measured after 20 min resting in the supine position ($r = -0.347$, $p < 0.05$). Clinical characteristics, including the presence of constipation, did not differ significantly between patients with and those without PPH.

Conclusions: In PD, systemic sympathetic denervation, impaired baroreflex-cardiovagal gain, and insufficiency of compensatory sympathetic nervous activation including lack of baroreflex-sympathoneural gain for postprandial splanchnic vessel pooling seem to be associated with PPH. Systemic sympathetic denervation and baroreflex failure seem to contribute to both pronounced morbidity and the development of PPH and OH.

1. Introduction

Postprandial hypotension (PPH) was first described in 1977 in a patient with Parkinson's disease (PD) [1]. Although increasing attention has focused on non-motor symptoms in PD, the mechanism of PPH in PD remains to be fully elucidated. In contrast, the mechanism of "orthostatic hypotension (OH)" has been examined by many investigators.

PPH has been defined as a fall in systolic blood pressure of ≥20 mmHg within 2 h of a meal. Geriatric patients [2], institutionalized elderly patients [3,4], and patients with diabetes [5] or end-stage renal disease who are receiving hemodialysis [6] are also known to be at high risk for PPH. Dizziness-lightheadedness is the most frequent clinical presentation, however, PPH has been also associated with syncope [7], falls [4,8], and even coronary events and stroke [9]. The maximum decrease in blood pressure (BP) typically occurs 35 min to 1 h postprandial [2,4,8], however, BP and symptoms should be monitored for 2 h postprandial, because the lowest recording in BP can occur up to 2 h postprandial [10]. The combination of PPH and OH in the postprandial period is considered to lead to more frequent hypotensive phenomena [11].

Patients with PD have a higher morbidity from OH than healthy people. OH is associated with sympathetic neurocirculatory failure [12] and is pronounced in more advanced PD patients [13]. Using a liquid food challenge to determine PPH in PD patients, it has been shown that there is only a moderate correlation between the degree of PPH and OH [14]. PPH is related to worsening of the parkinsonian state [15].

Thus, it would be expected that PPH was also associated with blunted sympathetic activation and clinical characteristics such as disease severity, motor phenotype, disease duration and the presence of constipation in addition to its high prevalence in patients with early-stage PD. However, studies looking at the relationship between PPH and catecholamine levels have yielded conflicting

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results [16,17]. Moreover, the relationship of PPH to insulin and glucose in patients with PD has not been investigated despite their known hypotensive effects [18,19]. We performed 75-g oral glucose tolerance tests, to investigate the mechanism and clinical characteristics of PPH in patients with de novo PD, using a method similar to that used in previous studies. We also examined the results of HUT testing to clarify similarities in the mechanisms of PPH and OH.

2. Methods

2.1. Subjects

We enrolled thirty seven patients with de novo PD. We also enrolled 10 age-matched healthy volunteers as controls. None of the patients had received levodopa or other anti-Parkinson drugs. PD was diagnosed clinically according to the diagnostic criteria of the UK Parkinson's Disease Society Brain Bank [20]. None of the subjects had abnormal findings on magnetic resonance imaging, such as brainstem or cerebellar atrophy. None had diabetes, end-stage renal disease, dehydration or symptoms of heart failure on cardiac echography or chest radiography. The severity of PD was assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. The patients were divided into tremor-dominant type (TDT), akinetic-rigid type (ART), and mixed type (MXT) subgroups by means of part III of the UPDRS in a manner similar to Spiegel and colleagues [21], on the basis of tremor and non-tremor scores. The tremor score was derived from the sum of UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands). The non-tremor score was obtained from the sum of UPDRS items 18 (speech), 19 (facial expression), 22 (rigidity), 27 (arising from chair), 28 (posture), 29 (gait), 30 (postural stability), and 31 (body bradykinesia and hypokinesia). PD was classified as TDT if the tremor score was at least twice the non-tremor score, as ART if the non-tremor score was at least twice the tremor score, or as MXT for the remainder. If patients were already receiving antihypertensive drugs including diuretics, these drugs were withdrawn for at least 48 h before they underwent the 75-g oral glucose tolerance testing and head-up tilt-table testing. This study was approved by the Ethics Committee of Jikei University School of Medicine, and all subjects gave written informed consent.

2.2. 75-g Oral glucose tolerance test (75-g OGTT)

After overnight fasting (except for non-caloric liquids), the subjects commenced the study between 9:00 am and 10:00 am. All subjects underwent testing in a quiet room, maintained at an ambient temperature of 23°–26° C. Wherever possible we performed HUT followed by 75-g OGTT on the same day. If this was not possible, the subjects underwent HUT and then 75-g OGTT the following day. After 20 min resting in the supine position, the subjects drank 75 g of glucose water (calorie content, 300 kcal) and remained resting and awake in the supine position for 120 min. After 20 min brachial systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and heart rate (HR, bpm) were measured by an automated sphygmomanometer in the supine position ($SBP_{PPH\ baseline}$, $DBP_{PPH\ baseline}$, $HR_{PPH\ baseline}$) and every 10 min for the next 120 min. The time to the maximum drop in SBP on the 75-g OGTT was also measured.

Plasma norepinephrine concentrations (NE, pg/ml) were measured after 20 min ($NE_{PPH\ baseline}$) and then every 30 min for to the next 120 min. Venous blood was drawn through a butterfly catheter. Differences in NE concentrations between each of the times of blood collection (after 30 min,, 60 min,, 90 min, and, 120 min) and the NE concentration after 20 min ΔNE_{PPH} ($\Delta NE\text{-}30_{PPH}$, $\Delta NE\text{-}60_{PPH}$, $\Delta NE\text{-}90_{PPH}$, $\Delta NE\text{-}120_{PPH}$) were calculated.

Plasma insulin concentrations (μU/ml) were also measured after 20 min ($Insulin_{baseline}$) and then every 30 min up to 120 min. As with the measurement of NE concentrations, plasma insulin concentrations were calculated after 20 min and the differences after 30, 60, 90, and 120 min (Δinsulin-30, Δinsulin-60, Δinsulin-90, Δinsulin-120) were calculated.

Similarly, plasma glucose concentrations (mg/dl) were measured after 20 min of rest in the supine position ($PG_{baseline}$), and the differences were calculated (ΔPG-30, ΔPG-60, ΔPG-90, ΔPG-120).

Postprandial hypotension was defined as a maximum decrease in SBP (ΔSBP_{PPH}) of ≥20 mmHg within 2 h after drinking the glucose.

2.3. Head-up tilt-table testing (HUT)

All subjects underwent HUT in a quiet room, maintained at an ambient temperature of 23°–26 °C. The subjects fasted overnight apart from non-caloric liquids, the studies commenced at 9:00 am. After 20 min of rest in the supine position, the subjects were tilted to a 60° upright position within 15 s by means of a head-up tilt tale. Brachial SBP, DBP, and HR were measured by an automated sphygmomanometer after 20 min of rest in the supine position ($SBP_{OH\ baseline}$, $DBP_{OH\ baseline}$, $HR_{OH\ baseline}$) and every 1 min after the subjects had been tilted for 10 min.

Plasma NE concentrations were also measured after 20 min of rest in the supine position ($NE_{OH\ baseline}$). Venous blood was drawn through a butterfly catheter.

OH was defined as a maximum decrease in SBP (ΔSBP_{OH}) of ≥20 mmHg.

2.4. Statistical analysis

Statistical analyses were performed using a statistical data analysis system (Esumi Co., Ltd, Tokyo, Japan). Differences between the groups were compared with the use of Welch's *t*-test for the continuous variables UPDRS motor score and disease duration. Pairwise comparisons were made using χ^2 tests for binary variables such as gender, motor phenotype, and the existence of constipation. Significant differences among controls, PD with PPH and PD without PPH were determined by the two-tailed multiple *t*-tests with Bonferroni correction following analysis of variance (ANOVA).

2.5. 75-g OGTT

Correlations of ΔSBP_{PPH} with $SBP_{PPH\ baseline}$, changes in plasma NE concentrations, changes in plasma insulin concentrations, changes in plasma glucose concentrations, the time at which SBP reached its lowest on 75-g OGTT, and ΔSBP_{OH} were assessed with the use of Spearman's rank correlation test. Correlations between the changes in plasma NE concentrations and the changes in plasma insulin concentrations were also determined using Spearman's rank correlation test.

2.6. HUT

Correlations between ΔSBP_{OH}, $SBP_{OH\ baseline}$ and $NE_{OH\ baseline}$ were determined using Spearman's rank correlation test.

P values of <0.05 were considered statistically significant.

3. Results

The clinical and laboratory data are summarized in Table 1. Six de novo PD patients had a diagnosis of hypertension. Of the healthy control subjects, 2 (20%) had PPH. Of the 37 patients with de novo PD, 17 (45.9%) had PPH, 15 (40.5%) had OH, and 8 (21.6%) had both PPH and OH. There was no significant difference in age, BMI, and HbA1c among controls, PD with PPH and PD without PPH. There was no significant difference in gender, UPDRS motor score, motor phenotype, disease duration and the presence of constipation between patients with and those without PPH.

3.1. 75-g OGTT

The absolute values comprising the mean SBP, DBP, HR NE, PG and insulin values are summarized in Table 2-A, Table 2-B and Fig. 1.

ΔSBP_{PPH} did not significantly correlate with clinical characteristics such as age, UPDRS motor score, or disease duration.

ΔSBP_{PPH} significantly correlated with $SBP_{PPH\ baseline}$ ($r = 0.394$, $p < 0.01$) (Fig. 2 a).

ΔSBP_{PPH} significantly negatively correlated with $NE_{PPH\ baseline}$ ($r = -0.347$, $p < 0.05$) (Fig. 2 b), but there was no correlation between the change of SBP and that of NE. Similarly, no correlation was found between the change of SBP and that of plasma insulin or glucose concentrations.

Table 1
The clinical characteristics of controls and patients with PD.

	Controls	PD without PPH	PD with PPH	*p* Value
Number	10 (2 with PPH)	20	17	
Age (range) (years)	74.3 ± 4.8 (64–79)	74.4 ± 7.5 (54–86)	76.8 ± 6.1 (63–86)	NS
BMI (kg/m^2)	23.0 ± 3.0	23.0 ± 3.4	21.5 ± 2.9	NS
HbA1c (NGSP) (%)	5.7 ± 0.3	5.7 ± 0.4	5.7 ± 0.4	NS
Sex (M:F)		8/12	4/13	NS
UPDRS motor score		20.0 ± 9.5	16.7 ± 12.1	NS
Subtype (ART/TDT or INT)		12/8	9/8	NS
Disease duration (years)		2.0 ± 2.7	2.7 ± 2.4	NS
Constipation		14	14	NS