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Systemic Postganglionic Adrenergic Studies Do Not Distinguish Parkinson's Disease From Multiple System Atrophy

Axel Lipp^{1,2}, Paola Sandroni¹, and Phillip A. Low^{1,*}

¹Department of Neurology, Mayo Clinic, Rochester, MN

²Department of Neurology, Charité - University Medicine Berlin, Germany

Abstract

Background—Multiple system atrophy (MSA) affects the preganglionic adrenergic neuron and Parkinson's disease (PD) involves the postganglionic counterpart. Widespread postganglionic denervation should result in denervation supersensitivity and a failure of the axon to release norepinephrine (NE). We examined if pharmacological dissection of the adrenergic neuron can distinguish between MSA and PD.

Method—We measured blood pressure, heart rate, and plasma NE responses to direct (phenylephrine) and indirect (tyramine) acting adrenergic agonists in 15 patients with probable MSA, 16 patients with idiopathic PD, and 16 age- and gender-matched controls.

Results—Baroreflex sensitivity was impaired in MSA and intact in PD. Pressor responses to phenylephrine (direct acting) were higher in MSA ($p < 0.01$) and PD patients ($p = 0.04$) than controls. Blood pressure responses to tyramine (indirect acting) were increased in MSA only ($p < 0.01$). Tyramine increased plasma catecholamine levels in all groups with no significant differences between groups.

Conclusion—There is denervation supersensitivity in PD patients that is, however, insufficient to shift the dose-response curve to the left. The excessive pressor responses to both tyramine and phenylephrine in MSA are due to baroreflex failure. We conclude that this diagnostic approach lacks sufficient sensitivity to differentiate PD and MSA.

Keywords

MSA; PD; baroreflex; tyramine; phenylephrine; autonomic; denervation supersensitivity

Introduction

Autonomic denervation occurs in both Parkinson's disease (PD) and multiple system atrophy (MSA). There is severe and generalized preganglionic adrenergic involvement in MSA [1]. In contrast the adrenergic lesion in PD is postganglionic [2,3]. In some organs, such as the heart, an evaluation of postganglionic adrenergic denervation will reliably distinguish PD from MSA [4-6]. Using directly acting adrenergic labels such as MIBG [4-6], hydroxyephedrine [7] or fluorodopa [8] uptake is uniformly reduced in PD and normal in MSA. It is of interest that

*To whom correspondence should be addressed: Mayo Foundation, Autonomic Reflex Laboratory, Department of Neurology, 200 First Street SW, Rochester, Minnesota 55905, Phone: 507-284-3375, Fax: 507-284-3133, Email: E-mail: low@mayo.edu.

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laboratory denervation occurs in the context of little clinical involvement. It is not known whether similar pharmacologic evidence of systemic adrenergic denervation occurs and if PD can be differentiated from MSA pharmacologically. We tested the hypothesis that systemic adrenergic pharmacologic dissection will similarly distinguish PD from MSA. It is well-known that a disorder with diffuse and severe postganglionic adrenergic involvement, such as pure autonomic failure (PAF), diabetic autonomic [9] or autoimmune autonomic neuropathy [10] will have denervation supersensitivity and a larger pressor response to directly acting adrenergic agonists, whereas a preganglionic disorder (MSA) will not [11]. Postganglionic denervation will result in receptor upregulation so that there will be a pressor response to subthreshold or low dose phenylephrine. The dose-response curve for a postganglionic disorder is shifted to the left and steeper, whereas the preganglionic disorder (MSA) is not shifted to the left but is steeper (due to baroreflex failure) [11,12]. We undertook pharmacologic dissection studies using a directly acting agonist, phenylephrine; and an indirectly acting agent (tyramine), which releases norepinephrine from intact postganglionic axons.

Methods

Subjects

The study cohort comprised fifteen patients with multiple system atrophy of the Parkinsonian type (MSA-P) according to the consensus criteria [1], sixteen patients with idiopathic Parkinson's disease, and sixteen age- and sex-matched, predominantly sedentary control subjects. The study was approved by the Institutional Review Board of the Mayo Clinic, and all subjects gave written informed consent before participation. Participants refrained from exercise, alcohol, and caffeine for 24 hours and from nicotine at least four hours. All vasoactive medication, including levodopa and fludrocortisone, was discontinued at least five half-lives before the study. Patients with concomitant conditions that potentially involve the CNS or affect autonomic testing (particularly diabetes, hypertension and coronary or congestive heart diseases) were excluded from the study. Prior to the study, all participants underwent clinical autonomic testing in order to assess cardiovagal (heart rate response to deep breathing), adrenergic (blood pressure responses to passive head up tilt and to Valsalva maneuver), and sudomotor (quantitative sudomotor axon reflex test - QSART, thermoregulatory sweat test - TST) function.

Measurements

Heart rate was measured by a three-lead electrocardiogram. Arterial blood pressure was measured on a beat-to-beat basis by finger photoplethysmography (Finometer model 1, FMS) and regularly verified by manual sphygmomanometry on the contralateral arm.

Protocol

Subjects were placed in a supine position and indwelling catheters were inserted into the cubital veins bilaterally for administration of vasoactive medication and to obtain blood samples. After a 20-minute period of quiet rest, heart rate, blood pressure, and respiration (chest expansion) were continuously recorded for a further 10-minute baseline period. To test for hemodynamic hypersensitivity to vasoactive agents, increasing dosages of tyramine (10, 20, and 30 mcg/kg) and phenylephrine (25, 50, 100, and 200 mcg) were administered at five minute intervals, but not before blood pressure returned to baseline. Trials were separated by a fifteen minute rest period and a subsequent ten minute baseline recording. Escalation of tyramine and phenylephrine boluses was stopped when blood pressure increased more than 30 mmHg or baseline systolic blood pressure exceeded 180 mmHg. Blood samples for plasma catecholamine levels were taken at baseline and 60 seconds after administration of tyramine boluses, respectively.

Data Acquisition and Data Analysis

Data were digitized with 14 bit resolution and a sample frequency of 500 Hz using WinDAQ data acquisition software (WinDAQ; Dataq Instruments, Akron, OH). R-R intervals, systolic and diastolic blood pressure, and respiration were analyzed offline with signal processing software (CODAS, Dataq Instruments, Akron, OH). Hemodynamic effects of vasoactive drugs were assessed as changes in systolic blood pressure and heart rate over baseline. To control for Finometer offset and recording artifacts, we also measured integrated blood pressure responses (area under the curve, AUC_{SBP}) over a 20 and 40 second period in response to phenylephrine and tyramine, respectively. Baroreflex sensitivity was assessed using the relationship between R-R interval and systolic blood pressure during phenylephrine boluses only, since the sequential administration of depressor and pressor agents (modified Oxford technique) would have confounded our primary analysis (pressor effect of phenylephrine/tyramine). To index the adrenergic component of the baroreflex we assessed blood pressure recovery time (BP-recovery time), defined as the time taken for systolic blood pressure to return to baseline (± 2 SD) after phenylephrine boluses.

All data are expressed as mean $\pm$ standard error of the mean. Phenylephrine induced changes in systolic blood pressure were compared between patients and controls by multiple-comparison analyses (unpaired t-test). Analysis of variance (one-way ANOVA) would not be appropriate in this regard, since differences between patients and controls but not within patients were considered (quod vide O'Brien, 1983) [13].

Results

Clinical characteristics

Clinical characteristics of patients and control subjects are summarized in Table 1. All patients exhibited parkinsonism, which was not or only minimally responsive to levodopa treatment in the case of MSA. Autonomic impairment (combined cardiovagal, adrenergic, sudomotor failure), scored using the Composite Autonomic Severity Scale (CASS) [14], was significantly higher in MSA, matching the criteria for probable MSA-P [1]. PD patients were slightly older than both MSA and control subjects, who in turn did not differ with respect to age. The severity of parkinsonism in MSA and PD patients was matched, although the Unified MSA Rating Scale (UMSARS) [15] was significantly higher in MSA than PD patients (Table 1); this reflects the fact that UMSARS measures also deficits such as oculomotor and cerebellar impairment in addition to extrapyramidal dysfunction.

Hemodynamic effects of vasoactive medication

Phenylephrine induced changes in systolic blood pressure were higher in patients than control subjects (Table 1, Fig. 1). In 8/16 PD and 10/15 MSA patients, however, administration of higher dosages of phenylephrine (100 and 200 mcg) was contraindicated due to resting supine hypertension and excessive blood pressure responses to lower doses. Thus, group-wise comparison was performed at a dose of 50 mcg phenylephrine. Blood pressure responses to phenylephrine were significantly higher in MSA (33.0 ± 4.6 mmHg) and PD (20.2 ± 1.8 mmHg) patients when compared to healthy controls (15.0 ± 1.4 mmHg; control vs. PD, $p = 0.04$; control vs. MSA, $p < 0.01$). The augmented pressor effect of phenylephrine in MSA and PD patients is even more pronounced when data are expressed as AUC_{SBP} (control: 147 ± 18 mmHg/20sec; MSA: 500 ± 77 mmHg/20sec; $p < 0.01$; PD: 288 ± 38 mmHg/20sec; $p < 0.01$). Tyramine increased systolic blood pressure in a dose-dependent fashion (Table 1, Fig. 2). Blood pressure response to 30 mcg/kg tyramine was not significantly different in PD patients and controls (PD: $AUC_{SBP} = 354 \pm 44$ mmHg/40sec, control: $AUC_{SBP} = 472 \pm 50$ mmHg/40sec, $p = 0.12$). In MSA, however, changes in arterial blood pressure exceeded those observed in controls significantly ($AUC_{SBP} = 996 \pm 98$ mmHg/40sec, $p < 0.01$).

Sensitivity of baroreflex control of heart rate

In the phenylephrine series, analysis of baroreflex control of heart rate (BRS) was significantly reduced in MSA patients only (control: 9.7 ± 1.1 msec/mmHg; MSA: 4.8 ± 0.7 msec/mmHg; $p < 0.01$). In PD, however, BRS did not differ from the control data set (PD: 8.9 ± 0.9 msec/mmHg; $p < 0.61$; Fig. 3). BP-recovery time after administration of phenylephrine boluses did not differ significantly between PD patients and controls (control: 38 ± 3 msec; PD: 63 ± 18 msec; $p = 0.12$, Fig. 4) and was overall independent from the phenylephrine dose used. In MSA, however, BP-recovery time was substantially delayed in a dose-dependent fashion (MSA: 147 ± 35 msec; $p < 0.01$; Fig. 4).

Plasma catecholamine levels

At baseline, plasma norepinephrine (NE) levels did not differ significantly between the groups, whereas plasma levels of the metabolite dihydroxyphenylglycine (DHPG) were significantly lower in patients (MSA and PD) compared to controls (data not shown). Intravenous administration of tyramine (30mcg/kg) induced a significant increase of DHPG in all groups (control: $+216 \pm 42$ pg/ml, $p < 0.01$; PD: $+172 \pm 58$ pg/ml, $p = 0.01$; MSA: 218 ± 41 pg/ml, $p < 0.01$), and of NE in control subjects only (control $p = 0.02$; PD $p = 0.9$ MSA $p = 0.07$). Between-group analysis (patients vs. controls) revealed no significant difference in tyramine induced catecholamine increase (Table 1).

Discussion

The main findings of the present study are as follows: there is an enhanced pressor response to the directly acting agonist, phenylephrine, in both PD and MSA but without a shift to the left in PD. The pressor response to indirect stimulation (tyramine) was increased in MSA only, while pressure responses in PD did not differ significantly from those seen in healthy controls. Baroreflex sensitivity is impaired in MSA and essentially intact in PD. We interpret these findings as follows: there is denervation supersensitivity in PD patients, but postganglionic denervation is insufficiently widespread to shift the dose-response curve to the left; the excessive pressor response to both tyramine and phenylephrine in MSA is due to baroreflex failure. We conclude that this diagnostic approach lacks sensitivity to differentiate PD and MSA.

The enhanced pressor response in MSA reflects baroreflex failure, mainly due to denervation of sympathetic neurons in the intermediolateral cell column [16] and C1 catecholaminergic neurons in the rostral ventrolateral medulla that has been extensively studied by our group [17-20] and others [11,12,21-23]. In our study, baroreflex failure was present in all MSA patients as indicated by severe orthostatic hypotension, impaired vagal baroreflex sensitivity and prolonged BP recovery time (Fig. 4). Accordingly, blood pressure responses to phenylephrine (50 mcg) and tyramine (30 mcg/kg) were significantly higher (Figs. 1 and 2) and longer lasting (BP-recovery time, Fig. 4) in MSA patients compared to controls because of this loss of baroreflex modulation.

The pattern of blood pressure responses observed in PD is rather complex with an augmented pressor response to direct but not indirect adrenergic stimulation. Our data are in good accordance to previous studies on PD, reporting increased blood pressure responses to direct acting agonists only (norepinephrine [24], isoprenaline [25]). The normal response to tyramine is concordant with the relatively intact vagal and adrenergic components of baroreflex and the absence of OH. Presumably the majority of postganglionic adrenergic axons remain physiologically intact.

In contrast to MSA, enhanced pressor responses to phenylephrine in PD are not caused by baroreflex failure. In these patients, autonomic reflex testing revealed a predominant postganglionic autonomic impairment with preserved baroreflex function. Both, baroreflex control of heart rate (Fig. 3) and blood pressure recovery time after phenylephrine boluses (Fig. 4) did not differ significantly between PD patients and controls. These findings are supported by earlier work of our group [19] and a more recent study on early PD [26], where baroreflex failure was limited to patients with concomitant OH. Conversely, Oka et al. [27] reported reduced baroreflex sensitivity in both, PD patient with and without OH, with a significant greater impairment within the first.

Indirectly acting sympathomimetic amines, which depend on the release of NE from neuronal stores, should no longer be active in syndromes with postganglionic adrenergic denervation such as PD. Partial denervation however may result in intermediate states in which there may be enhancement of responses to indirectly acting sympathomimetic amines [11]. In our present study, blood pressure response to tyramine did not differ between PD patients and controls. Similar results were obtained in patients with a more widespread postganglionic denervation (pure autonomic failure - PAF) [11], where blood pressure response to tyramine was even increased.

We therefore conclude that the increased pressor response to sympathomimetic amines in MSA and PD is caused by different lesions within the autonomic network. In MSA, excessive blood pressure perturbations are predominantly induced by baroreflex failure. In PD, increased pressor responses are caused in part by denervation supersensitivity, a phenomenon most autonomic effector organs develop in response to chronic postganglionic efferent denervation [28]. Accordingly, excessive pressor responses to adrenergic stimuli were also demonstrated in other syndromes with concomitant peripheral autonomic impairment, such as diabetic autonomic (distal small-fiber) neuropathy [29], migraine [30], and thoracic spinal cord transection [31].

In Polinsky's study [11], denervation supersensitivity was indicated by a left-shift of the dose-response curve while impaired baroreflex buffering resulted in an increased slope. In our present study, however, we failed to demonstrate a left-shift of the dose-response curve in PD for various reasons. First, to avoid a simultaneous activation of cardiac β_1 -adrenoreceptors, we used the highly selective α_1 -adrenoreceptor agonist phenylephrine instead of NE [11,24,25,32]. Hence, pressor responses to phenylephrine were excessively increased in most MSA and PD patients, contraindicating administration of higher dosages (100 and 200 mcg). Consequently, we were compelled to analyze single-dose responses rather than dose-response curves. Second, due to the anticipated high pressor responses in MSA, maximum dose of tyramine was limited to 30mcg/kg; a dosage probably insufficient to induce considerable blood pressure responses in PD patients and controls. In a comparable study on PAF patients, tyramine was administered up to 80mcg/kg and no significant blood pressure effect was observed at dosages below 30mcg/kg [11]. In a series of PD patients [32], the median dose of tyramine necessary to increase systolic blood pressure by 20 and 30 mmHg was 43 and 69 mcg/kg, respectively. Third, we did not control our tyramine preparation for possible dopamine contamination as discussed by Jacob and Goldstein [33]. Commercially available tyramine solutions frequently contain 0.7 to 1.0% of dopamine that causes vasodilation and thus might dampen the pressor response to tyramine boluses. Fourth, the concurrence of reduced norepinephrine release but normal blood pressure response to tyramine would further support our notion of denervation supersensitivity in PD. In the present study, tyramine induced increase in plasma norepinephrine and DHPG levels did not differ significantly between groups. However, quantitative assessment of norepinephrine kinetics using the isotope dilution method [34] would certainly be more reliable to detect minor differences in norepinephrine spillover following tyramine administration between groups.

In conclusion, reduced neurotransmission in postganglionic autonomic fibers of PD patients appeared to be counteracted in part by an increased postsynaptic sensitivity. This denervation supersensitivity is not suitable for an early differentiation of Parkinson etiologies (PD vs. MSA). However, PD patients might be at risk of excessive blood pressure alterations in response to commonly used dosages of vasoactive substances.

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Figure 1.

Dose-dependent changes in systolic blood pressure (mean $\pm$ SEM) in response to intravenous administration of phenylephrine (25 to 200mcg) expressed as area under the curve (20 sec. window). Administration of 100 and 200mcg phenylephrine was contraindicated in several MSA (10/15, filled circle) and PD (7/15, open circle) patients due to resting supine hypertension. Since corresponding results are biased by sample selection, group-wise analysis was limited to a dose of 50 mcg phenylephrine (shaded area). Controls (asterisk).

Figure 2.

Dose-dependent changes in systolic blood pressure (mean $\pm$ SEM) in response to intravenous administration of tyramine (10, 20, and 30 mcg/kg). Analysis was limited to dosage of 30 mcg/kg of tyramine (shaded area). Controls (asterisk), PD (open circle), MSA (filled circle).

Figure 3.

Individual data and average values (mean $\pm$ SEM) for sensitivity of baroreflex control of heart rate (R-R interval) during phenylephrine boluses. Baroreflex sensitivity was significantly reduced in MSA ($p < 0.01$, filled circle) whereas PD patients (open circle) did not differ from controls (asterisk).

Figure 4.

Individual data of blood pressure recovery time. The period systolic blood pressure needed to return to baseline after phenylephrine bolus (50mcg) was significantly increased in MSA ($p < 0.01$, filled circle) only. Control (asterisk), PD (open circle).

Table 1
Hemodynamic parameters and plasma catecholamine levels at baseline and in response to vasoactive medication (mean ± SE, unpaired t-test controls vs. patients; *PD vs. MSA).

Parameters	Units	Control	PD	P (C vs. PD)	MSA	P (C vs. MSA)
Baseline						
N		16	16		15	
Age	years	60 ± 2.1	67 ± 2.2	p = 0.03	62 ± 2.1	p = 0.5
Gender	f : m	6 : 10	7 : 9		7 : 8	
BMI	kg/m ²	27 ± 0.9	27 ± 1.2	p = 0.9	27 ± 0.7	p = 0.9
Duration	month		52 ± 11		7 ± 3	p < 0.01*
UMSARS	points		12.5 ± 1.6		22.4 ± 2.2	p < 0.01*
CASS	points	1.4 ± 0.8	2.8 ± 0.6	p < 0.01	5.1 ± 0.3	p < 0.01
Phenylephrine 50 mcg						
N		14	10		11	
AUC _{SBP}	mmHg/20sec	147 ± 18	288 ± 38	p < 0.01	500 ± 77	p < 0.01
BP-recovery	msec.	38 ± 3	63 ± 18	p = 0.18	147 ± 357	p < 0.01
Tyramine 30 mcg/kg						
N		13	8		12	
AUC _{SBP}	mmHg/40sec	472 ± 50	354 ± 44	p = 0.12	995 ± 98	p < 0.01
ΔPlasma NE	pg/ml	+33 ± 13	0 ± 19	p = 0.14	+41 ± 19	p = 0.9
ΔPlasma DHPG	pg/ml	+216 ± 42	+172 ± 58	p = 0.53	+218 ± 41	p = 0.83