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Arterial Baroreflex Dysfunction Fails to Mimic Parkinson's Disease in Rats

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Abstract. Patients with Parkinson's disease (PD) often have attenuated baroreflex function, which may occur before the onset of PD-associated movement disorders. The aim of the present study was to test whether impaired arterial baroreflex (ABR) function could contribute to the pathogenesis of PD. 6-Hydroxydopamine (8 μg in 4 μl) was microinjected into the left substantia nigra of rats to establish unilateral PD models, and bilateral PD models were established in rats by administration of rotenone by osmotic minipump for four weeks, at a dose of 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$. An ABR dysfunction model was obtained by performing sinoaortic denervation (SAD). Hemodynamic variables were determined in conscious rats. PD-like symptoms and dopamine content in corpus striatum (CS) were also assessed. 6-Hydroxydopamine and rotenone treatment and SAD were associated with enhanced blood pressure variability (BPV) and blunted baroreflex sensitivity (BRS). Rotenone, but not SAD, significantly reduced dopamine content in the CS, induced catalepsy, and inhibited rearing and exploratory behavior. SAD before the administration of rotenone did not aggravate the rotenone-induced dopaminergic lesion. Our findings do not support the presumption that ABR dysfunction contributes to the pathogenesis of PD in rats.

Keywords: arterial baroreflex, Parkinson's disease, baroreflex sensitivity, blood pressure variability, sinoaortic denervation

Introduction

The arterial baroreflex (ABR) is a dominant mechanism in short term control of arterial pressure. Its function may be expressed as baroreflex sensitivity (BRS) and can be abolished by sinoaortic denervation (SAD) (1 – 3). Sinoaortic-denervated animals exhibit persistent high blood pressure variability (BPV) without a sustained elevation in mean arterial blood pressure (BP) (4). Recently, many studies focused on the relationship between the ABR dysfunction and the pathogenesis and poor prognosis of many cardiovascular diseases such as acute myocardial infarction, chronic heart failure, stroke, endotoxic shock, ventricular arrhythmia, and atherosclerosis (5 – 10). In many cases, ABR dysfunction is the cause leading to a poor prognosis of many cardiovascular diseases (8 – 10).

Autonomic nervous system dysfunction, including gastrointestinal disorders and cardiovascular dysfunction, is common in patients with Parkinson's disease (PD) (11, 12). For example, orthostatic hypotension is a common symptom of cardiovascular dysfunction in patients with PD, which appears to arise from a combination of vasomotor-, cardiac sympathetic-, and baroreflex-dysfunction (13). Importantly, attenuated baroreflex function in PD may even precede the behavioral and motor symptoms of PD (14, 15). To our knowledge, no studies have focused on the effects of ABR dysfunction on behavior and motor function.

In the current study, we tested the presumption that baroreflex dysfunction contributes to the pathogenesis of PD. We determined whether SAD in rats induces PD-like behavioral and motor deficits and depletion of dopamine content in the corpus striatum (CS) or aggravate the rotenone-induced dopaminergic lesion. Parallel studies were performed in rats treated with 6-hydroxy-

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dopamine or rotenone to establish PD models. ABR function of two kinds of rat model of PD was also investigated.

Materials and Methods

Animals

Male Sprague-Dawley rats weighing 270 – 300 g were provided by Sino-British SIPPR/BK Laboratory Animal (Shanghai, China). They were housed with controlled temperature (22°C – 25°C) and lighting (8:00 – 20:00 light, 20:00 – 8:00 dark) and allowed free access to tap water and standard rat chow. All the animals used in this experiment received humane care in compliance with institutional guidelines for health and care of experimental animals.

6-Hydroxydopamine-induced PD models

Under the guidance of a stereotaxic apparatus (MD-3000; Bioanalytical Systems Incorporation, West Lafayette, IN, USA), a micropipette (tip diameter of 20 – 30 μm) was inserted into the left substantia nigra (bregma: −5.3 mm, lateral: 1.8 mm, ventral, −7.8 mm) (16) of a rat anesthetized with a combination of ketamine (50 mg/kg) and diazepam (5 mg/kg). The micropipette was filled with 6-hydroxydopamine (2 μg/μl; Sigma Chemical Company, St. Louis MO, USA) or its vehicle (0.02% Vitamin C diluted in 0.9% saline) in a volume of 4 μl. The injection rate was 1 μl/min (17). The successful establishment of PD models was verified by measurement of the rotation induced by apomorphine (0.5 mg/kg diluted in 0.9% saline, s.c.; Sigma) (18). Rats rotating at least 200 turns in 30 min were considered to be successful models.

Rotenone-induced PD models

Osmotic minipumps (Model 2ML4; Alzet Osmotic Pumps Company, Cupertino CA, USA) was implanted subcutaneously between the scapulae of rat anesthetized with ketamine and diazepam. Rotenone (2.5 $mg \cdot kg^{-1} \cdot day^{-1}$, Sigma) or its vehicle (dimethyl sulfoxide and polyethylene glycol, 1:1; both from Sigma) were administered subcutaneously by an osmotic minipump (19).

SAD-induced baroreflex dysfunction

Rats underwent SAD according to a method described previously (1 – 3). Briefly, rats were anesthetized with ketamine and diazepam and were then medicated with atropine sulfate (0.5 mg/kg, i.p.) and procaine benzylpenicillin (60,000 U, i.m.). After a midline neck incision and bilateral isolation of the neck muscles, aortic baroreceptor denervation was performed bilaterally by cutting the superior laryngeal nerves near the vagi, removing the superior cervical ganglia, including a small section of the sympathetic trunk, and sectioning the aortic depressor nerves. The carotid sinus baroreceptors were denervated bilaterally by stripping the bifurcation and its branches, followed by application of 10% phenol (in 95% ethanol) to the external, internal, and common carotid arteries and the occipital artery. Other rats underwent a sham operation. This included a midline neck incision and bilateral isolation of the neck muscles. Animals were allowed to recover spontaneously after the operation. Rat mortality after SAD was 20% and occurred within 1 week. No death occurred after sham operation.

Experimental protocols

Section 1: At 4 weeks after microinjection of 6-hydroxydopamine or its vehicle, when 6-hydroxydopamine-induced nigrostriatal dopaminergic lesions had been stable, rotational behavior of rats was tested. Measurement of arterial BP and BRS (see below) was then carried out in the successful PD models (n = 8) and the control group (n = 10).

Section 2: Rotenone (n = 35) or its vehicle (n = 9) were administered for four weeks. Behavioral testing (see below) and measurement of BP and BRS was then carried out. Rats were then killed by cervical dislocation and the dopamine content of their corpus striata was determined (see below).

Section 3: Rats were studied at 2 weeks after SAD (n = 10) or sham surgery (n = 12), when SAD-induced ABR dysfunction had been stable. As for section 2, all animals were subjected to behavioral testing, BP and BRS measurement, and post-mortem determination of CS dopamine content. Same experiments were performed on rats at 66 weeks after SAD (n = 21) or sham surgery (n = 24) to study the long-lasting effect of ABR dysfunction.

Section 4: Rotenone was administered to SAD (n = 24) or sham-operated (n = 25) rats, from the third week after operation, for four weeks. Behavioral testing was then carried out, and CS dopamine content was determined.

Behavioral testing

The tests for catalepsy were conducted on a bar which was 9-cm-above, and parallel to the base. The rats were placed with both front paws on the bar in a half rearing position. The time taken for at least one paw to be actively displaced from the bar (descent latency) was determined. The maximum descent latency was fixed at 180 s (20, 21). For the open field test, each animal was placed into the open field, a square wooden box (80 cm × 80 cm × 40 cm). A fan provided ventilation

and the box was lit by a 25-W red bulb. The floor of the box was divided into 25 equal-sized squares (16 cm × 16 cm). The movement and behavior of the rats was recorded by video and later quantified off-line. The number of times each rat crossed a line demarcating adjacent squares and the number of times each rat reared in 3 min were recorded.

BP measurement

Systolic BP (SBP), diastolic BP (DBP), and heart period (HP) were recorded continuously using the previously described technique (22, 23). Briefly, rats were anesthetized with a combination of ketamine and diazepam. A polyethylene catheter was inserted into the lower abdominal aorta via the left femoral artery for BP measurement and another catheter was inserted into left femoral vein for intravenous injection. The catheters were exteriorized through the interscapular skin. After a two-day recovery period, the animals were placed in individual cylindrical cages containing food and water. The aortic catheter was connected to a BP transducer via a rotating swivel that allowed the animals to move freely in the cage. After a 4-h habituation period, the BP signal was digitized by a microcomputer. SBP, DBP, and HP values from each heart beat were determined on line. The mean values of these parameters during a period of 4 h were calculated. The standard deviation over the mean was defined as the quantitative parameter for SBP variability (SBPV), DBP variability (DBPV), and HP variability (HPV).

BRS measurement

At the conclusion of the 4-h period of measurement of basal BP, BRS was measured in the conscious rat using a previously described method (24). The principle of this method is to measure the prolongation of HP in response to an elevation of SBP. A bolus injection of phenylephrine was used to induce a BP elevation. The dose of phenylephrine (5 – 10 μg/kg) was adjusted to raise SBP by about 30 mmHg. HP was plotted against SBP for linear regression analysis; the slope of SBP–HP was expressed as BRS (ms/mmHg).

Assay of dopamine content

The animals were killed by cervical dislocation. CS was immediately dissected out free on ice, weighed, and then homogenized in ice-cold 0.1 M perchloric acid (5 μl/mg of wet weight) containing 0.1 mM ethylenediamine tetraacetic acid (EDTA). Homogenates were centrifuged at 20,000 × g for 20 min at 4°C. The supernatant was filtered and stored at −80°C prior to assay. Content of dopamine in the CS was then quantitatively measured using high performance liquid chromatography with electrochemical detection. The column was 3.0 mm ID × 150 mm (MD-150; ESA Biosciences Incorporation, Chelmsford MA, USA). The mobile phase (pH = 3) comprised 90 mM sodium dihydrogen phosphate, 50 mM citric acid, 1.7 mM 1-octanesulfonic acid sodium salt, 50 μM EDTA, and 10% acetonitrile.

Statistical analyses

Data are each expressed as the mean ± S.D. Differences between two groups were evaluated by Student's unpaired t-test. $P<0.05$ was considered statistically significant.

Results

Hemodynamic variables of 6-hydroxydopamine–treated rats

As shown in Table 1, unilateral microinjection of 6-hydroxydopamine did not significantly affect SBP, DBP, HP, or HPV. However, SBPV (+25%, $P<0.05$) and DBPV (+22%, $P<0.05$) were greater in 6-hydroxydopamine-induced rat models of PD than in control rats, while BRS was markedly less (−49%, $P<0.01$).

Hemodynamic variables and dopamine content in CS of rotenone-treated rats

Nigrostriatal dopaminergic lesions occurred in 10 of 35 rotenone-treated rats, and CS dopamine content of the 10 rats was 71% less than that in the control group ($P<0.01$, Table 2). Similar to findings in 6-hydroxydopamine–induced rat models of PD, rotenone-treatment did not significantly affect SBP, DBP, HP, or HPV. However, SBPV (+52%, $P<0.01$) and DBPV (+46%, $P<0.01$) were greater in rotenone-treated rats than in control rats, while BRS was markedly less (−55%, $P<0.01$).

Effects of rotenone-treatment on behaviors in rats

As presented in Fig. 1a, descent latency in the catalepsy test was significantly greater in rotenone-treated rats than in vehicle-treated control rats ($P<0.01$). The number of line crossings (−63%, $P<0.05$) and rearings (−62%, $P<0.05$) in the open field test was less in the rotenone-treated rats than control rats (Fig. 1: b and c).

Hemodynamic variables and dopamine content in CS of SAD rats

As shown in Table 3, at either 2 or 66 weeks after operation, SAD rats exhibited significantly greater BPV (SBPV and DBPV) and markedly lower BRS, when compared with age-matched sham-operated rats. However there were no significant differences in SBP, DBP, HP, and HPV between SAD and sham-operated

Table 1. Effects of unilateral microinjection of 6-hydroxydopamine on hemodynamic variables of rats

	Control (n = 10)	6-OHDA (n = 8)
SBP (mmHg)	124 ± 9	126 ± 9
DBP (mmHg)	84 ± 6	82 ± 7
HP (ms)	172 ± 11	176 ± 15
SBPV (mmHg)	6.7 ± 1.2	8.4 ± 1.6*
DBPV (mmHg)	5.9 ± 0.9	7.2 ± 1.3*
HPV (ms)	11.9 ± 2.1	11.3 ± 2.4
BRS (ms/mmHg)	0.93 ± 0.38	0.47 ± 0.13**
Number of rotations	0	327 ± 54**

6-OHDA: 6-hydroxydopamine; SBP, DBP: systolic and diastolic blood pressure, respectively; HP: heart period; SBPV, DBPV, and HPV: SBP, DBP, and HP variability, respectively; BRS, baroreflex sensitivity. Mean ± S.D. *P<0.05, **P<0.01 *vs* control group.

Table 2. Effects of rotenone-treatment on hemodynamic variables and dopamine content in the corpus striatum of rats

	Control (n = 9)	Rotenone (n = 10)
SBP (mmHg)	126 ± 13	122 ± 12
DBP (mmHg)	86 ± 9	83 ± 10
HP (ms)	177 ± 13	174 ± 11
SBPV (mmHg)	6.4 ± 1.1	9.7 ± 1.9**
DBPV (mmHg)	5.7 ± 0.8	8.3 ± 1.5**
HPV (ms)	13.9 ± 1.7	14.2 ± 2.3
BRS (ms/mmHg)	0.96 ± 0.43	0.43 ± 0.11**
Dopamine (ng/mg)	7.48 ± 0.68	2.14 ± 0.23**

Abbreviations are as for Table 1. Mean ± S.D. **P<0.01 *vs* control group.

rats. There was also no significant difference in CS dopamine content between SAD and sham-operated rats, at either 2 or 66 weeks after surgery.

Effects of SAD on behaviors in rats

There were no significant differences, between SAD and sham-operated rats, in either descent latency in the catalepsy test or the number of line crossings and rearings in the open field test (Figs. 2 and 3).

Effects of prior SAD on rotenone-induced nigrostriatal dopaminergic lesion in rats

Rotenone treatment induced nigrostriatal dopaminergic lesions in 7 of 24 SAD rats, and 7 of 25 sham-operated rats. All the 14 rats exhibited similar PD-like symptoms with that in rotenone-induced rat models of PD in section 2. There were no significant difference in dopamine content of the lesioned CS between SAD and sham-operated rats (2.07 ± 0.29 *vs* 2.12 ± 0.26 ng/mg).

Discussion

This is the first report to demonstrate the effects of ABR dysfunction on behavior and motor function, although our observations do not support the presumption that ABR dysfunction contributes to the pathogenesis of PD in rats.

Previous investigators have observed ABR dysfunction in PD, which may precede the development of behavioral and motor symptoms of PD (14, 15). These clinical observations provided the impetus for our current investigation of the potential for SAD-induced ABR dysfunction to cause PD. The ABR is a major regulatory mechanism in the cardiovascular system. To study ABR function, we used SAD to interrupt the ABR arc. In the current study, SAD rats exhibited an impaired baroreflex function characterized by lower BRS and higher BPV, as described previously in a range of mammalian species (4). Nevertheless, neither the typical behavioral characteristics of PD observed in rotenone-treated rats nor a depletion of dopamine content in CS was observed in SAD rats. SAD may reduce the concen-

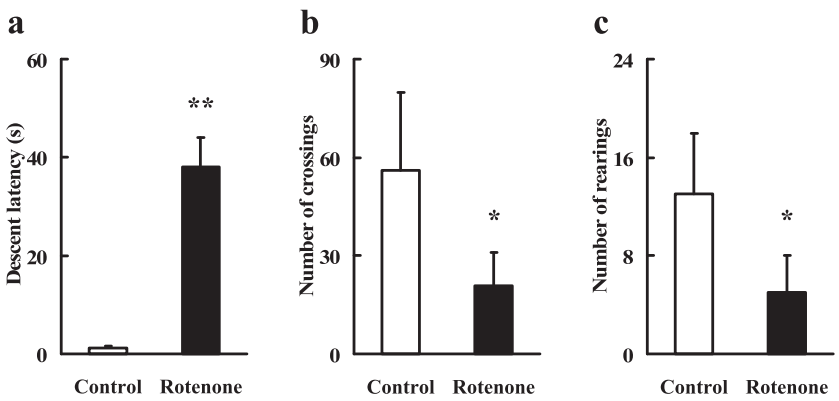

Fig. 1. Effects of rotenone-treatment on behaviors characteristic of Parkinson's disease in rats. a: Descent latency in the catalepsy test; b: number of line crossings in the open field test; c: number of times rats reared during the open field test. n = 10 in the rotenone group, and n = 9 in the control group. Data are expressed as means ± S.D. *P<0.05, **P<0.01 *vs* vehicle control.

Table 3. Effects of sinoaortic denervation on hemodynamic variables and dopamine content in the corpus striatum of rats at 2 and 66 weeks after surgery

	2 weeks		66 weeks	
	Control (n = 12)	SAD (n = 10)	Control (n = 24)	SAD (n = 21)
SBP (mmHg)	132 ± 9	130 ± 10	135 ± 10	135 ± 12
DBP (mmHg)	86 ± 8	88 ± 8	88 ± 9	89 ± 10
HP (ms)	169 ± 12	165 ± 13	183 ± 10	180 ± 12
SBPV (mmHg)	6.5 ± 1.2	13.8 ± 4.1**	7.1 ± 1.3	14.5 ± 4.0**
DBPV (mmHg)	5.2 ± 0.8	11.7 ± 2.9**	5.8 ± 1.0	12.6 ± 3.2**
HPV (ms)	14.9 ± 2.2	15.3 ± 2.4	14.6 ± 2.5	14.3 ± 2.3
BRS (ms/mmHg)	0.94 ± 0.41	0.26 ± 0.14**	0.81 ± 0.34	0.21 ± 0.12**
Dopamine (ng/mg)	7.49 ± 0.62	7.38 ± 0.54	6.75 ± 0.56	6.54 ± 0.58

SAD, sinoaortic denervation; other abbreviations are as for Table 1. Mean ± S.D. **P<0.01 *vs* control group.

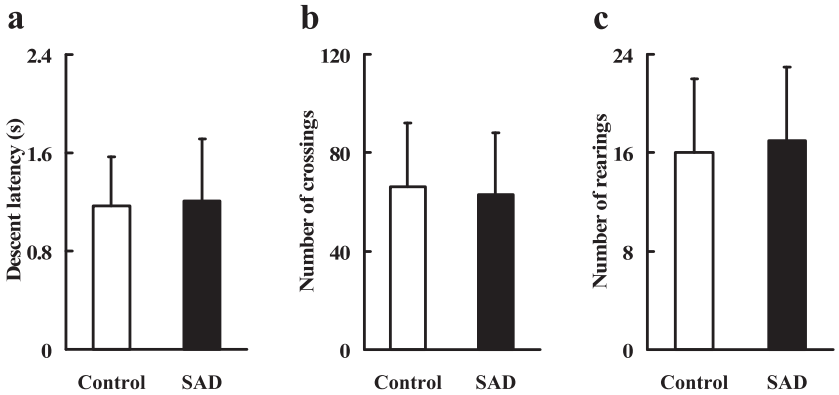

Fig. 2. Effects of sinoaortic denervation (SAD) on behaviors characteristic of Parkinson's disease in rats at 2 weeks after surgery. a: Descent latency in the catalepsy test; b: number of line crossings in the open field test; c: number of times rats reared during the open field test. n = 10 in the SAD group and n = 12 in the control group. Data are expressed as means ± S.D.

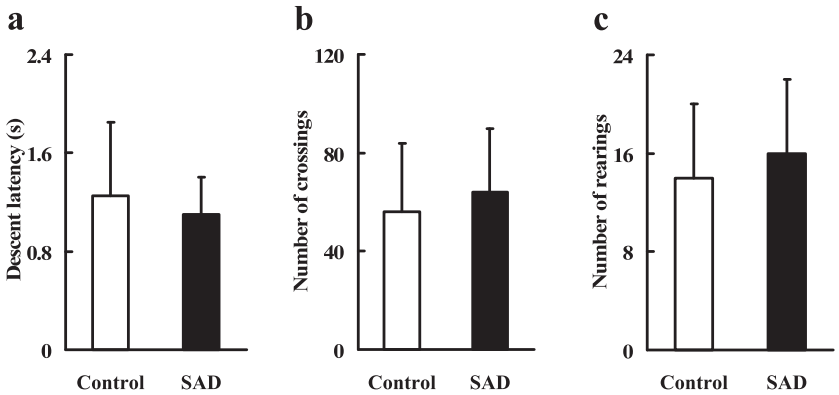

Fig. 3. Effects of sinoaortic denervation (SAD) on behaviors characteristic of Parkinson's disease in rats at 66 weeks after surgery. a: Descent latency in the catalepsy test; b: number of line crossings in the open field test; c: number of times rats reared during the open field test. n = 21 in the SAD group and n = 24 in the control group. Data are expressed as means ± S.D.

tration of dopamine released from synapsis in CS as a short-term effect (25). Nevertheless, in the long term, SAD does not influence the whole striatal dopamine content, which represents the dopamine content in substantia nigra indirectly.

In our study, prior SAD did not aggravate the rotenone-induced dopaminergic lesion: 1) there was no difference in success rate of rotenone-induced PD models between SAD and sham-operated rats (29.2% *vs* 28.0%) and 2) PD-like symptoms and reduced CS dopamine content that represented the severity of nigrostriatal dopaminergic lesions were the same in the two groups of rats. All the above-mentioned observations showed that ABR dysfunction could not cause PD and it even does not contribute to the pathogenesis of PD in rats.

PD is a late-onset, progressive neurodegenerative disorder characterized by selective nigrostriatal dopamin-

ergic degeneration and Lewy body formation (26, 27). Both genetic and environmental factors are implicated in PD pathogenesis (28). Rotenone is a commonly used pesticide and potent, highly specific inhibitor of complex I. Chronic rotenone exposure reproduces features of PD (19, 29). This was confirmed in our current study, in that rotenone-treated rats displayed typical behavioral characteristics of PD in the catalepsy and open field test and a substantial depletion of dopamine (about –71%) in the CS.

6-Hydroxydopamine is a kind of specific catecholaminergic neurotoxin. Unilateral injection of 6-hydroxydopamine into the nigrostriatal pathway is widely used to establish a hemi-PD model in rats (30). It was reported that the nigrostriatal dopamine pathway may mediate BRS through the efferent parasympathetic pathway in the medulla of rats (31). In this study, both 6-hydroxydopamine- and rotenone-treated rats exhibited a significant decrease in BRS and an increase in BPV, which indicated baroreflex dysfunction, without any change in BP, HP, or HPV. These results support findings of previous studies that patients with PD often have baroreflex failure (14 – 16, 32, 33). The present study shows baroreflex dysfunction in both of the two rat models of PD, which opens up the possibility of future studies aiming to clinically distinguish primary ABR dysfunction from that sharing a common pathogenesis with PD.

In summary, ABR dysfunction fails to mimic the typical behavioral characteristics and depletion of dopamine content in CS of PD in rats. Both 6-hydroxydopamine- and rotenone-treated rats may be applied as PD models in research to improve the outcome and survival of PD patients with co-existing cardiovascular disease.

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