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Crucial Role of Nifedipine on Stabilizing Blood Pressure in Sinoaortic Denervated Rats

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Abstract
Background: The present work was designed to investigate the possible synergism of nifedipine and captopril, nifedipine and atenolol, and nifedipine and hydrochlorothiazide on lowering and stabilizing blood pressure (BP) in sinoaortic-denervated (SAD) rats.
Methods: Fifty-six SAD rats were randomly divided into 7 groups. They were respectively given nifedipine (3.0 mg/kg), captopril (100 mg/kg), atenolol (10 mg/kg), hydrochlorothiazide (20mg/kg), and combined nifedipine and other three drugs. The drugs were given via a catheter in a gastric fistula. BP was recorded for 5h from 1h before drug administration to 4h after administration, in conscious, freely moving rats.
Results: It was found that combination of nifedipine and others three drugs much significantly decreased BP and BP variability than these drugs alone. The *q* values calculated by probability sum analysis were all between 1.20 and 2.50 for SBP, DBP, SBPV and DBPV for the combination of nifedipine and others three drugs.
Conclusion: The present work clearly demonstrated that there is a synergistic effect between nifedipine and captopril, nifedipine and atenolol, and nifedipine and hydrochlorothiazide in lowering and stabilizing the BP. Nifedipine made the crucial role on lowering and stabilizing the BP in SAD.

Keywords: Nifedipine, Blood pressure, Blood pressure variability, Sinoaortic-denervated

Introduction

Blood pressure (BP) is not constant and there exists a spontaneous variation. This variation is defined as blood pressure variability (BPV). BPV is increased in both hypertensive human beings and hypertensive animals [1-3]. Furthermore, BPV is positively related to the severity of organ damage in hypertensive humans and rats [4–6]. In other words, increased BPV can produce organ damages. Therefore, it has been proposed that an antihypertensive drug with a BP-stabilizing effect would benefit the hypertensives additionally. Several works of our department have demonstrated that long-term treatment with ketanserin, candesartan, nitrendipine, the combination of amlodipine and atenolol, and irbesartan and amlodipine not only decreased BP level, but also decreased BPV, and had obvious effects on organ protection in spontaneously hypertensive rats (SHR) as well. The organ protection was importantly attributed to the decrease in BPV [7–10].

The main function of arterial baroreflex is to maintain the stability of blood pressure [11]. The baroreflex arc may be interrupted by sinoaortic denervation or completely lesion of the nucleus tractus solitarius [12, 13]. In these animals with baroreflex dysfunction, BPV is dramatically high [14, 15]. So, several laboratories including our own use sinoaortic denervated animals as models of high BPV to study the pathology and pharmacology of pressure lability.

Clinically, combination therapy against hypertension using two or more drugs from different classes can produce better drug efficacy [16]. Furthermore, the use of such synergistic therapy is also recommended for the initial treatment of hypertension [17]. It has reported [18] that nifedipine significantly decreased blood pressure variability in SAD rats. It is speculated that the combination of nifedipine and others drugs will produce a synergistic effect to decreasing BPV. Therefore, this study was designed to investigate the synergistic effects of the combination of nifedipine and others drugs on lowering and stabilizing BP in SAD rats.

Materlals and Methods

Animals and Drugs

Male Sprague-Dawley rats were provided by Sino-British SIPPR/BK Lab Animal Ltd (Shanghai, China). They were housed with controlled temperature (22-25 ºC) and lighting (8AM to 8PM light, 8PM to 8AM dark) and with free access to tap water and rat chow. All procedures were in accordance with institutional animal care guidelines.

Nifedipine, hydrochlorothiazide and captopril were purchased from Sigma Chemical Co. (St. Louis, Missouri, USA). Atenolol was provided by Shanghai Second Pharmaceutical Co. (Shanghai, China). Nifedipine and hydrochlorothiazide were dissolved in the 0.5% carboxymethylcellulose sodium (CMC). Captopril and atenolol were dissolved in pure water. The doses were used as follows: nifedipine 3 mg/kg, captopril 100 mg/kg, atenolol 10mg/kg, hydrochlorothiazide 20mg/kg and 3+100mg/kg, 3+10mg/kg, 3+20mg/kg combination of the nifedipine and other drugs. Drugs were administered by intra-gastric catheter implanted 3 days before.

Sinoaortic Denervation

At the age of 10-11 weeks, sinoaortic denervation was performed in Sprague-Dawley rats according to the method previously described [19, 20]. Briefly, rats were anesthetized with a mixture of ketamine (50 mg/kg) and diazepam (5 mg/kg) intraperitoneally. Atropine sulfate (0.5 mg/kg) was then administered intraperitoneally. Each animal was fixed in supine position and a 2.5 cm midline incision was made in the neck. After bilateral isolation of the neck muscles, aortic baroreceptor denervation was carried out bilaterally by cutting the superior laryngeal nerves near the vagi, removing the sympathetic trunk, and sectioning aortic depressor nerves. The carotid sinus baroreceptors were denervated bilaterally by stripping the carotid bifurcation and its branches, followed by application of 10% phenol in 95% ethanol solution to the external, internal, and common carotid arteries and the occipital artery [19, 20]. The incision was sutured closed and each rat was injected intramuscularly with 60000 units of penicillin G.

Blood Pressure Measurement

Four weeks after sinoaortic denervation, rats were anesthetized as above-mentioned. A polyethylene catheter (PE-10 connected to PE-50) was chronically inserted into the lower abdominal aorta via the left femoral artery for the measurements of BP and heart period (HP), and another catheter (PE-50) was inserted into the left femoral vein for the examination of baroreflex function, the third catheter (PE-50) was inserted into the stomach for drug administration [21, 22]. These catheters were tunneled subcutaneously, exteriorized between the scapulae, and fixed on saddle. After 2 days of recovery, BP was continuously recorded in conscious unrestrained rats with a computerized technique [21, 23]. Briefly, the BP signals, transmitted to the electric signals by a transducer, were digitized and processed on a personal computer, which calculated on line the BP and HP beat by beat. The average value was used as an index of BP, and the standard deviation (SD) of beat-to-beat BP values as an index of BPV [21, 23]. The same method was used for the calculation of HP. In SAD rats, arterial baroreflex function for heart rate control was also assessed by intravenous injection of phenylephrine 2 to 5 μg/kg. If SAD rats exhibit a bradycardia of less than 20 beats/min, they were considered as successful baroreceptor denervation and included in the study [24, 25].

Protocol

After about 4-h habituation to BP recording environment, the BP signal was recorded for half an hour as the basal (pre-drug) value. Then, the drug was administered via the catheter of gastric fistula. One and half an hour after administration of the drug, the BP signal was recorded for half an hour as post-drug value.

Probability Sum Test

To determine whether the drugs were acting synergistically, we used the probability sum test. This test comes from classic probability analysis and is useful for evaluating the synergistic interactions between two drugs (q test) [10, 21].

In the present work, we used the following criteria. Compared with the mean values from control rats, treated rats with a decrease in BP (SBP or DBP) $\geq$ 20 mmHg were defined as responders and rats with a decrease in BP < 20 mmHg were defined as non-responders. For BPV (SBPV or DBPV), the criterion was 2 mmHg. The formula used is as follows: $q=P_{A+B}/(P_A+P_B-P_A\times P_B)$. Here, A and B indicate drug A and drug B; P (probability) is the percentage of responders in each group. P_{A+B} is the real percentage of responders and ($P_A+P_B-P_A\times P_B$) is the expected response rate. P_A+P_B is the sum of the probabilities when drug A and drug B is used alone. $P_A\times P_B$ is the probability of rats responding to both drugs when they were used alone. When $q<0.85$, the combination is antagonistic, when $q>1.15$, the combination is synergistic, and when q is between 0.85 and 1.15, the combination is additive.

Statistical Analysis

Data were expressed as mean ± SE. Comparisons between values obtained in the same group before and after drug administration were made using the paired t - test. $P < 0.05$ was considered statistically significant.

Results

Effects of nifedipine, captopril, atenolol and hydrochlorothiazide alone on BP and HP after sinoaortic denervation in rats

The effects of nifedipine, captopril, atenolol and hydrochlorothiazide alone on BP and HP in conscious SAD rats are summarized in Table 1. It was found that SBP and DBP were significantly decreased in all groups treated with nifedipine, captopril, atenolol or hydrochlorothiazide alone. HP was significantly prolonged by atenolol but not changed by other three drugs in SAD rats.

Effects of nifedipine in combination with captopril, atenolol or hydrochlorothiazide on BP and HP after sinoaortic denervation in rats

As shown in Table 1, the BP reduction in conscious SAD rats was more pronounced in the combination of nifedipine with captopril, atenolol or hydrochlorothiazide than in nifedipine or captopril, atenolol, hydrochlorothiazide alone. Nifedipine in combination with captopril, atenolol or hydrochlorothiazide induced greater decrease in SBP （-34, -38, -27 mmHg） than nifedipine (-23 mmHg) or captopril (-26 mmHg), atenolol (-13mmHg), hydrochlorothiazide (-9 mmHg) alone. In terms of DBP, the results obtained were similar to those for SBP. The prolongation in HP induced by atenolol was attenuated by adding nifedipine.

Table 2 illustrated the synergistic effect of nifedipine in combination with captopril, atenolol or hydrochlorothiazide on BP. The q values were 1.25, 1.78, 1.75 for SBP and 1.64, 1.66, 1.33 for DBP respectively when combing nifedipine with captopril, atenolol or hydrochlorothiazide.

Effects of nifedipine, captopril, atenolol and hydrochlorothiazide alone on BPV after sinoaortic denervation in rats

The effects of nifedipine, captopril, atenolol and hydrochlorothiazide alone on BPV after SAD in rats were shown in Figure 1. It was found that although nifedipine, captopril, atenolol and hydrochlorothiazide alone significantly decreased SBP and DBP as shown in Table 1, the values of SBPV and DBPV were unchanged by both captopril and hydrochlorothiazide. However, significant decreases of BPV were found in groups treated with both nifedipine (10.7 ± 1.3 mmHg before versus 9.0 ± 1.0 mmHg after drug administration for SBPV and 9.5 ± 1.2 mmHg versus 7.3 ± 0.8 mmHg for DBPV) and atenolol (10.1 ± 1.0mmHg versus 8.0 ± 0.5mmHg for SBPV and 8.6 ± 0.8mmHg versus 6.8 ± 0.5mmHg for DBPV) in SAD rats.

Effects of nifedipine in combination with captopril, atenolol or hydrochlorothiazide on BPV after sinoaortic denervation in rats

Combination of nifedipine and captopril, atenolol or hydrochlorothiazide dramatically decreased SBPV and DBPV in conscious SAD rats. Significant decreases in SBPV and DBPV were found in groups treated with combination of nifedipine and captopril (10.1 ± 1.9 mmHg versus 5.9 ± 0.6

mmHg and 8.0 ± 0.8 versus 4.8 ± 0.4 mmHg), nifedipine and atenolol (10.1 ± 1.0mmHg versus 8.0 ± 0.5mmHg and 8.6 ± 0.8mmHg versus 6.8 ± 0.5mmHg) or nifedipine and hydrochlorothiazide (10.9 ± 1.5 mmHg versus 6.7 ± 0.4 mmHg and 9.7± 1.5 versus 4.8 ± 0.4 mmHg). The BPV reductive effects of the combination of nifedipine and other three drugs were more significantly than any of them alone (Figure 1). From Table 2, we can also find the synergistic effect of nifedipine in combination with captopril, atenolol or hydrochlorothiazide on BPV. For the combination of nifedipine and captopril, atenolol or hydrochlorothiazide, the q values were 2.00, 1.60 or 2.50 for SBPV, and 1.38, 1.23 or 2.00 for DBPV.

Table1: Effects of nifedipine (Nif), captopril (Cap), atenolol (Ate) and hydrochlorothiazide (Hyd) alone and interactive combination on blood pressure and heart period (HP) after sinoaortic denervation in rats. SBP, systolic blood pressure; DBP, diastolic blood pressure; Before, before drug administration; After, after drug administration. $n = 8$ in each group. Mean ± SE. $^{**}P < 0.01$ *vs* Before.

Groups	Doses (mg/kg)	SBP (mmHg)		DBP (mmHg)		HP (ms)	
		Before	After	Before	After	Before	After
Nif	3	138 ± 4.3	115 ± 3.2**	96 ± 3.2	77 ± 1.8**	151 ± 3.6	142 ± 5.0
Cap	100	138 ± 2.8	112 ± 2.1**	93 ± 1.8	69 ± 2.1**	140 ± 6.1	143 ± 5.0
Ate	10	141 ± 3.2	128 ± 3.9**	95 ± 3.6	81 ± 4.3**	158 ± 5.0	182 ± 3.2**
Hyd	20	137 ± 3.9	128 ± 4.3*	98 ± 4.3	91 ± 3.9*	150 ± 4.3	146 ± 4.3
Nif + Cap	3 + 100	135 ± 3.6	101 ± 3.2**	91 ± 3.2	56 ± 3.2**	142 ± 5.4	141 ± 4.3
Nif + Ate	3 + 10	146 ± 4.3	108 ± 5.0**	97 ± 3.6	68 ± 5.4**	142 ± 3.6	163 ± 4.3**
Nif + Hyd	3 + 20	140 ± 2.5	113 ± 1.8**	89 ± 3.2	70 ± 2.5**	136 ± 4.3	132± 3.9

Table 2: Results of probability sum tests for the combination of nifedipine (Nif) and captopril (Cap), nifedipine (Nif) and atenolol (Ate) and nifedipine (Nif) and hydrochlorothiazide (Hyd) on blood pressure and blood pressure variability after sinoaortic denervation in rats. SBP P, percentage of responders for systolic blood pressure; DBP P, percentage of responders for diastolic blood pressure; SBPV P, percentage of responders for systolic blood pressure variability; DBPV P, percentage of responders for diastolic blood pressure variability. $n = 8$. $q = P\text{Nif+Cap}/(P\text{Nif} + P\text{Cap} - P\text{Nif} \times P\text{Cap})$. If $q<0.85$, the combination is antagonistic, if $q>1.15$, the combination is synergistic, if q is between 0.85 and 1.15, the combination is additive.

Groups	Dose(mg/kg)	SBP P	DBP P	SBPV P	DBPV P
Nif	3	4/8	3/8	2/8	3/8
Cap	100	4/8	3/8	2/8	1/8
Nif + Cap	3 + 100	8/8	8/8	7/8	5/8
q values		1.25	1.64	2.00	1.38
Nif	3	4/8	3/8	2/8	3/8
Ate	10	1/8	1/8	4/8	3/8
Nif + Ate	3 + 10	8/8	6/8	8/8	6/8
q values		1.78	1.66	1.60	1.23
Nif	3	4/8	3/8	2/8	3/8
Hyd	20	0/8	0/8	0/8	0/8
Nif + Hyd	3 + 20	7/8	4/8	5/8	6/8
q values		1.75	1.33	2.50	2.00

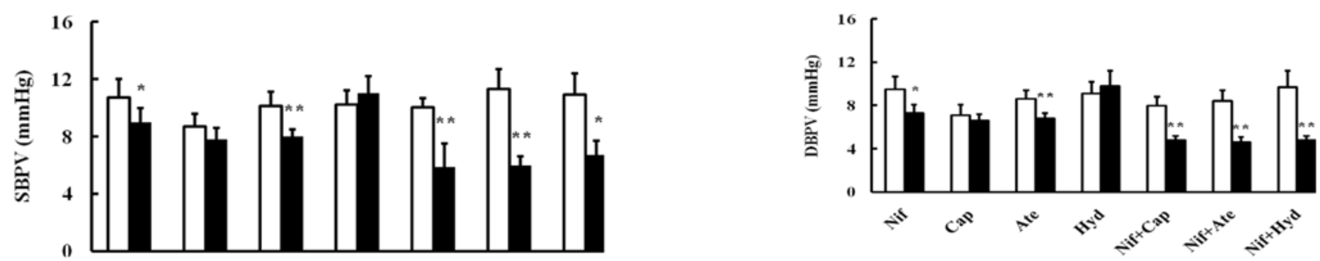

Fig 1: Effects of nifedipine (Nif), captopril (Cap), atenolol (Ate) and hydrochlorothiazide (Hyd) alone and interactive combination on blood pressure variability in sinoaortic-denervated rats (SAD, n=8). SBPV and DBPV are the standard deviations of systolic blood pressure and diastolic blood pressure; □, before drug administration; ■, after drug administration. Data were expressed as mean ± SE. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with before drug administration.

Discussion

In clinic, the purpose that using fixed-dose combinations of 2 different kinds of antihypertensive drugs in the treatment of hypertension is to obtain increased BP control and to enhance compliance by using a single tablet that is taken once or twice daily [26]. Furthermore, by combining 2 different agents at lower doses, the clinical and metabolic side effects that would be produced by either drug at higher doses can be minimized [27]. Therefore, fixed-dose combinations of antihypertensive drugs could potentially increase BP control, simplify dosage regimens, improve compliance, decrease dose-dependent side effects, and reduce costs as the first-line treatment for hypertension [28]. These advantages make it recommendable for the combination antihypertensive therapy to be used as initial treatment, particularly in patients with end-organ damage (EOD) or more severe initial hypertension [29, 30].

However, high BP is not a unique factor determining hypertensive EOD. It is recently suggested that BPV is an important determinant for end-organ damage in hypertension [4, 31]. BPV is an independent cardiovascular risk factor, and reduction of BPV might be considered as a new strategy for the treatment of hypertension [15, 32]. Therefore, antihypertensive drugs, which reduced BP with the ability of decreasing BPV, will produce additional benefit for hypertensive patients. We have previously proposed two ways to reduced BPV in antihypertensive therapy [6]: (1) to find antihypertensive drugs with an intrinsic effect on lowering BPV, such as ketanserin, adenosine analogues, and so on; and (2) to treat with the long-acting antihypertensive drugs, such as candesartan, amlodipine, and so on. The present work might show a third way to control BPV in the treatment of hypertension: combination therapy.

During the past four decades, several classes of agents, such as calcium channel blockers, angiotensin-coverting enzyme inhibitors, β-blockers and diuretics have been shown to effectively reduce elevated blood pressure and associated cardiovascular events [33-36]. It is well known that nifedipine possesses a rapid and relatively short-lasting antihypertensive action. But the present work for the first time systematically studied and clearly demonstrated the synergism on BPV reduction of nifedipine when combined with atenolol, captopril or hydrochlorothiazide. We found that the q values for SBPV and DBPV after combination of nifedipine and captopril were 2.00 and 1.38, respectively. The q values for SBPV and DBPV after combination of nifedipine and atenolol were 1.60 and 1.23. The q values for SBPV and DBPV after combination of nifedipine and hydrochlorothiazide were 2.50 and 2.00. The synergism on BPV reduction in nifedipine combination therapy might attribute to the differences in the hemodynamic features and hypotensive mechanisms between nifedipine and the other 3 drugs.

In conclusion, the combination of nifedipine and another drug atenolol, captopril or hydrochlorothiazide has a significant synergistic effect on lowing BP and stabilizing BPV in SAD. Furthermore, nifedipine made a crucial role on lowing and stabilizing BP in SAD in combination therapy.

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