Baroreflex sensitivity differs among same strain Wistar rats from the same laboratory

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Abstract

Previous studies showed that a proportion of normotensive Sprague-Dawley rats spontaneously exhibit lower baroreflex sensitivity. However, investigations have not yet been carried out on Wistar rats. We aimed to compare baroreflex sensitivity among rats from the same strain and the same laboratory. Male Wistar normotensive rats (300-400g) were studied. Cannulas were inserted into the abdominal aortic artery through the right femoral artery to measure mean arterial pressure and heart rate. Baroreflex was calculated as the derivative of the variation of heart rate in function of the mean arterial pressure variation (ΔHR/ΔMAP) tested with a depressor dose of sodium nitroprusside (50 µg/kg) and with a pressor dose of phenylephrine (8µg/kg) in the right femoral venous approach through an inserted cannula. We divided the rats into four groups: i) high bradycardic baroreflex, baroreflex gain less than -2 tested with phenylephrine; ii) low bradycardic baroreflex, baroreflex gain between -1 and -2 tested with phenylephrine; iii) high tachycardic baroreflex, baroreflex gain less than -3 tested with sodium nitroprusside; and iv) low tachycardic baroreflex, baroreflex gain between -1 and -3 tested with sodium nitroprusside. Approximately 71% of the rats presented a decrease in bradycardic reflex while around half showed an increase in tachycardic reflex. No significant changes in basal mean arterial pressure and heart rate, tachycardic and bradycardic peak and heart rate range were observed. There was a significant change in baroreflex sensitivity among rats from the same strain and the same laboratory.

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Introduction

The baroreflex (BR) or baroreceptor reflex is one of the body's homeostatic mechanisms to maintain blood pressure. It provides a negative feedback loop in which the elevated blood pressure reflexively causes blood pressure to decrease; similarly, the decreased blood pressure depresses the baroreflex, causing blood pressure to rise. The system relies on specialized neurons (baroreceptors) in the aortic arch, carotid sinuses and elsewhere to monitor changes in blood pressure and relay them to the brainstem. Subsequent changes in blood pressure are mediated by the autonomic nervous system.[1] Over the past 20 years, it has been reported that arterial baroreflex function is significantly related to the prognosis of acute cardiovascular infarction, arrhythmias, heart failure and stroke in humans.[2-5] Clinical observations indicate that patients with a lower BR show shorter survival times with these diseases. It was reported that arterial baroreflex function plays an important role in the pathogenesis and prognosis of hypertension, atherosclerosis, aconitine-induced arrhythmia and LPS-induced shock.[6,7] In addition, BR is helpful in the diagnosis and prognosis of cardiac diseases.[4]

It has been shown that a fraction of normotensive Sprague-Dawley rats spontaneously exhibit lower baroreflex sensitivity.[6,8] Furthermore, previous studies from our group demonstrated that baroreflex gain (BG) differs between juvenile spontaneously hypertensive rats,[9] adult[10] and young[11] Wistar Kyoto rats from the same laboratory. However, no study has yet investigated if there is a difference in baroreflex sensitivity between Wistar rats from the same laboratory. Therefore, in this study we compared the baroreflex sensitivity among conscious Wistar rats in order to verify if there are differences between strains.

Materials and Methods

Animals

The experiments were performed on Wistar rats (300-400 grams) from the same laboratory. Rats were housed individually in plastic cages under standard laboratory conditions. They were kept under a 12 h light/dark cycle (lights on at 06:30 h) and had free access to food and water. Housing conditions and experimental procedures were approved by the Institution's Animal Ethics Committee and the experimental procedures employed conform to the accepted principles of how animals are

used in biomedical science. Efforts were made to minimize the number of animals used.

Surgical preparation

One day before the experiments, the rats were anesthetized with ketamine (50 mg/kg i.p.) and xylazine (50 mg/kg i.m.) and a catheter was inserted into the abdominal aorta through the femoral artery to allow blood pressure and heart rate (HR) to be recorded. Catheters were made of 4 cm segments of PE-10 polyethylene (Clay Adams, USA) heat bound to a 13 cm segment of PE-50. The catheters were tunneled under the skin and exteriorized at the animal's dorsum.[9]

Arterial pressure and heart rate recording in conscious rats

Approximately 24 h after surgery, the animals were transported in individual cages to the room where the experiments were carried out. Animals were allowed 20 min to adapt to the conditions of the room, such as sound and illumination, before blood pressure and heart rate recordings began. The experimental room was acoustically isolated and had constant background noise produced by an air exhauster. At least another 15 min were allowed before beginning experiments. Pulsatile arterial pressure (PAP) of freely moving animals was recorded using an HP-7754A preamplifier (Hewlett Packard, USA) and an acquisition board (MP100A, Biopac Systems Inc, USA) connected to a computer. Mean arterial pressure (MAP) and heart rate (HR) values were obtained from the PAP recordings and processed on-line.[9]

Baroreflex test

The baroreflex was tested with a pressor dose of phenylephrine (PHE, bolus 8 μg/kg IV; Sigma Chemical) and depressor doses of sodium nitroprusside (SNP, bolus 50 μg/kg IV; RBI). The baroreflex was calculated as the derivation of HR in function of the MAP variation (ΔHR/ΔMAP). There was an interval of at least 15 min between the infusions to allow basal values to recover. We also evaluated bradycardic and tachycardic peak, HR range, and the difference between bradycardic and tachycardic peak and sympathetic (SBG) and parasympathetic baroreflex gain (PBG).[9] Rats were divided into groups according to baroreflex gain (BG): i) high bradycardic baroreflex (HB), BG less than -2 tested with PHE; ii) low bradycardic baroreflex (LB), BG between -1 and -2 tested with PHE; iii) high tachycardic baroreflex (HT), BG less than -3 tested with SNP; and iv) low tachycardic baroreflex (LT), BG between -1 and -3 baroreflex sensitivity tested with SNP.

Statistical analysis

Values are reported as the means ± standard error of means (S.E.M.). HR, MAP, ΔHR, ΔMAP, bradycardic and tachycardic peak, HR range, SBG and PBG were compared between HB and LB groups as well as between HT and LT groups. Distributions were then evaluated through the Kolmogorov normality test, Student's t-test was used to verify differences between normal distributions, and the Mann-Whitney test was applied to assess differences between non-parametric distributions. In order to verify the association of age and weight with baroreflex function, Pearson's correlation test was used. Differences were considered significant when the probability of a Type I error was less than 5% ($P<0.05$).

Results

Based on baroreflex gain tested with PHE, of the 34 Wistar rats evaluated approximately 29% presented higher baroreflex gain (HB group; < -2 bpm/mmHg). On the other hand, a large number of the group presented lower baroreflex gain according to testing with PHE (LB group; between -1 and -2 bpm/mmHg).

In order to verify whether another cardiovascular parameter would differ between the HB and the LB groups, we compared baseline MAP and HR, bradycardic and tachycardic peak, HR range, SBG and PBG. No significant difference was observed between these two groups regarding basal MAP and HR, bradycardic and tachycardic peak, or HR range and the sympathetic component of baroreflex gain (Table 1). However, there was a significant difference in the parasympathetic component of baroreflex gain.

There was no difference in PHE-induced increase in MAP between the HB and the LB groups ($P=0.6858$). Nevertheless, bradycardic reflex responses to intravenous PHE was significantly decreased in the LB group ($P<0.0001$) (Figure 1).

Recordings obtained during baroreflex testing with PHE in conscious rats of the HB and the LB groups showed a clear difference in bradycardic reflex between the two groups and similar responses to PHE-induced increase in arterial pressure (Figure 2).

We also compared SNP-induced decrease in MAP and tachycardic responses to i.v. SNP between the HB and the LB groups. MAP decrease in response to SNP was similar between the groups ($P=0.7824$) and tachycardic responses to MAP decrease tended to be reduced in the HB group, but this did not reach statistical significance ($P=0.2338$) (Figure 3). Representative recordings taken during baroreflex testing with SNP in one rat from the HB group and one from the LB group are shown in Figure 4. It is interesting to note the similar responses to SNP-induced decrease in MAP and the tendency for a reduction in tachycardic reflex in the HB group. When baroreflex gain was tested with SNP, we observed that among the 33 Wistar rats analyzed, approximately 54% presented a tachycardic baroreflex gain below -3 bpm/mmHg while the others (around 46%) presented a tachycardic baroreflex gain of between -1 and -3 bpm/mmHg. Baseline MAP and HR, bradycardic and tachycardic peak, HR range, and SBG and PBG were compared between the HT and the LT groups. Significant differences were only observed with respect to the sympathetic component of the baroreflex gain (Table 2). There was no significant difference between the two groups regarding basal MAP and HR, bradycardic and tachycardic peak, or HR range and the sympathetic component of baroreflex gain. A comparison of PHE-induced increase in MAP between the HT and the LT groups showed no significant difference ($P=0.705$). Furthermore, there was no difference in bradycardic reflex responses to increases in arterial pressure between the two groups ($P=0.567$) (Figure 5). Recordings obtained during baroreflex testing with PHE in conscious rats of the HT and the LT groups showed no clear difference in PHE-induced

Table 1. Baseline level of mean arterial pressure (MAP) and heart rate (HR), bradycardic and tachycardic peak, HR range, sympathetic (SBG) and parasympathetic baroreflex gain (PBG) in HB (n=10) and LB (n=24) groups.

Variable	HB	LB	P
MAP (mmHg)	108.3±2.43	108.07±2.49	0.5734
HR (bpm)	326.56±9.38	319.87±7.89	0.5778
Bradycardic peak (bpm)	229.39±12.44	226±8.74	0.2178
Tachycardic peak (bpm)	464.72±10.87	490.13±6.89	0.7786
HR range (bpm)	240.5±12.89	259±6.4	0.3105
PBG (bpm x $mmHg^{-1}$)	-1.71±0.09	-1.92±0.16	<0.0001
SBG (bpm x $mmHg^{-1}$)	-3.23±0.28	-2.86±0.15	0.524

increase in arterial pressure and bradycardic reflex between the two groups (Figure 6).

Decreases in MAP in response to SNP were similar between the HT and the LT groups (P=0.451) (Figure 7). However, tachycardic reflex responses to decreases in arterial pressure were significantly reduced in the LT group (P<0.0001). Representative recordings obtained during baroreflex testing with SNP in one rat from the HT group and one from the LT group are shown in Figure 8. It is interesting to note the similar responses to SNP-induced decreases in MAP and reduced tachycardic responses in the LT group. Correlation analysis was performed to verify the association of age and weight with baroreflex function. However, there was no significant correlation between age and parasympathetic (r=0.2; P>0.05) and sympathetic baroreflex (r=0.13; P>0.05) or between weight and parasympathetic (r=0.23; P>0.05) and sympathetic baroreflex (r=0.11; P>0.05).

Discussion

We had previously reported a difference in baroreflex gain among young Wistar Kyoto[11] and spontaneously hypertensive rats[9] and adult[10] Wistar Kyoto rats from the same laboratory. Therefore, the present study aimed to compare baroreflex function among Wistar rats using bolus infusion of the vasopressor PHE and the vasodepressor SNP. Rats from the same strain and the same laboratory could be divided into two groups according to baroreflex gain. Comparison between these two groups showed that the parasympathetic component of the baroreflex gain and bradycardic reflex response to increase in arterial pressure were significantly reduced in approximately 71% of the rats studied. Moreover, the sympathetic component of the baroreflex gain and tachycardic reflex in response to a decrease in arterial pressure were significantly reduced in approximately 46% of the rats. The lack of signs of pain or discomfort suggests that stress or pain after surgery did not influence the outcomes of the experiments.

The baroceptor reflex was estimated in our study by bolus infusion and we verified HR changes in response to arterial pressure increase or reduction caused by i.v. infusion of SNP or PHE, respectively. According to our findings, approximately 71% of 34 Wistar rats (LB group) presented reduced bradycardic reflex response to an increase in arterial pressure and decreased baroreflex gain tested with the α1-adrenergic agonist PHE. However, when we compared basal MAP and HR, bradycardic and tachycardic peak, HR range and baroreflex gain tested with SNP no

Table 2. Baseline level of mean arterial pressure (MAP) and heart rate (HR), bradycardic and tachycardic peak, HR range, and sympathetic (SBG) and parasympathetic baroreflex gain (PBG) in the HT (n=18) and the LT (n=15) groups.

Variable	HB	LB	P
MAP (mmHg)	109.1±4.12	110.1±1.9	0.9409
HR (bpm)	333.1±19.2	365.3±12.7	0.3503
Bradycardic peak (bpm)	229.39±12.44	226±8.74	0.6409
Tachycardic peak (bpm)	456.42±11.26	483.32±8.6	0.732
HR range (bpm)	232.6±13.23	243±7.6	0.2521
PBG (bpm x mmHg^{-1})	-1.82±0.1	-1.83±0.2	0.9494
SBG (bpm x mmHg^{-1})	-3.34±0.19	-2.01±0.1	<0.0001

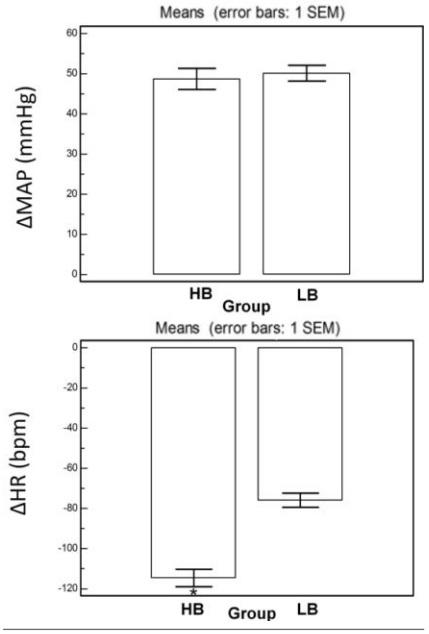

Figure 1. Increase in mean arterial pressure (MAP, mmHg) and decrease in heart rate (HR, bpm) in response to phenylephrine (PHE, 8μg/kg i.v.) in the HB (n=10) and the LB groups (n=24). *P<0.0001: difference to the LB group.

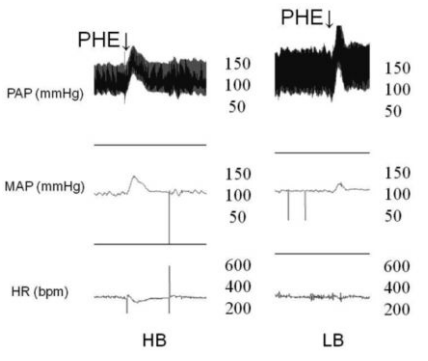

Figure 2. Recordings from one rat from the HB group and one from the LB group showing reflex bradycardia (top) in response to increases in blood pressure. Infusions were given in bolus. MAP, mean arterial pressure; PAP, pulsatile arterial pressure; HR, heart rate; PHE, phenylephrine.

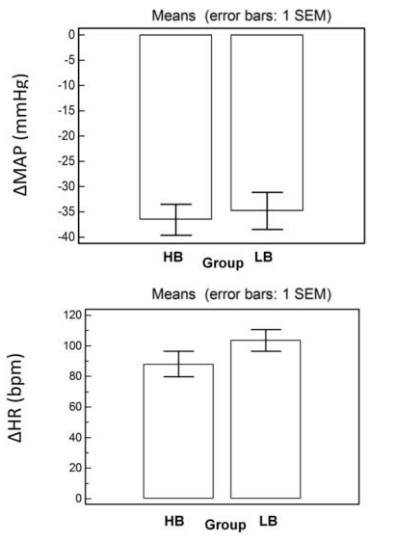

Figure 3. Decrease in mean arterial pressure (MAP, mmHg) and decrease in heart rate (HR, bpm) in response to sodium nitroprusside (SNP, 50 μg/kg i.v.) in the HB (n=10) and the LB groups (n=24).

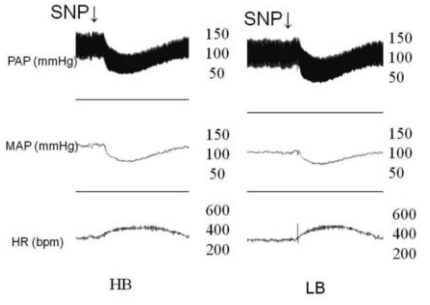

Figure 4. Recordings from one rat from the HB group and one from the LB group showing reflex tachycardia (top) in response to decreases in blood pressure. Infusions were given in bolus. MAP, mean arterial pressure; PAP, pulsatile arterial pressure; HR, heart rate; SNP, sodium nitroprusside.

significant differences were observed. Our findings suggest that a large number of Wistar rats present impaired gain of reflex bradycardia, the parasympathetic component of baroreflex sensitivity, while a small number presented significant increased gain of the reflex bradycardia. The mechanisms that cause the reduction in baroreflex function are not completely understood.[10] Some studies have demonstrated that the carotid body is significantly larger in rats with impaired baroreflex,[11-13] whereas other studies have indicated that the decreased baroreflex function is due to impaired levels of norephinephrine, epinephrine and dopamine in the carotid body[13-15] and medulla oblongata areas that regulate the cardiovascular system.[16] Furthermore, there have been reports that AT1 (angiotensin) receptor densities are also involved in models of damaged baroreflex function.[17,18] It is possible that such mechanisms are involved in the changes in baroreflex function among those rats of the same strain.

Our results show that around half of the animals presented a significant increase in gain of the reflex tachycardia and the other half presented a significant reduction in gain of the reflex tachycardia. Great attention has been focused on the role of the sympathetic activity regarding the onset of hypertension in a genetic model (spontaneously hypertensive rats, SHR). Previous studies have shown that there is a rise in sympathetic drive to the vessels in adult SHR and have suggested that this is important for the maintenance of increased blood pressure.[19,20] It is possible that this rise in sympathetic output is not primarily a consequence of changes in either baroceptor reflex[20] or chemoreflex function but is rather a product of a change in the central neural circuitry involved in generating the sympathetic output.[21] In view of these considerations, although there was no significant change in basal MAP and HR between the groups, the possibility remains that rats with increased tachycardic reflex are more likely to present higher sympathetic nerve activity. However, this was not measured in our study and future investigation is needed to confirm this hypothesis.

Reports in the literature indicate that changes in vascular reactivity is an important marker of hypertension.[22,23] No significant difference was observed with respect to PHE-induced increase in arterial pressure and blood pressure reduction in response to SNP. We may suggest that, although there is an explicit difference between rats of the same strain (Wistar) in bradycardic and tachycardic reflex in response to increases and decreases in blood pressure, respectively, there is no significant difference in α1-adrenergic receptor activation located at the smooth muscle cells (stimulated with phenylephrine) and its response to nitric oxide (stimulated with sodium nitroprusside). In our research, the baroreflex function was evaluated in conscious rats, since baroreflex activity is impaired under anesthesia[24,25] reducing the range of HR. Therefore, only a limited proportion of the baroreflex response could be analyzed. We believe our investigation provides reliable information about the differences in baroreflex function among rats of the same strain. It would also be interesting to compare this cardiovascular reflex between other strains of rats, such as SHR stroke prone (SHRSP), and between other animals, such as rabbit and mouse.

Some aspects of our investigation should be addressed. We recognize the limitations in our evaluation of baroceptor reflex in that we were unable to provide a full baroreflex function curve. Nevertheless, the baroceptor reflex values obtained from our study are of physiological importance since they fall around the operating point of this reflex in an unrestrained conscious rat.[26] In accordance with our routine procedure, the animals' food and drink intake were not quantified over the first 24 h after surgery. On the other hand, we did verify whether the animals were hungry or thirsty before the experiments. The point

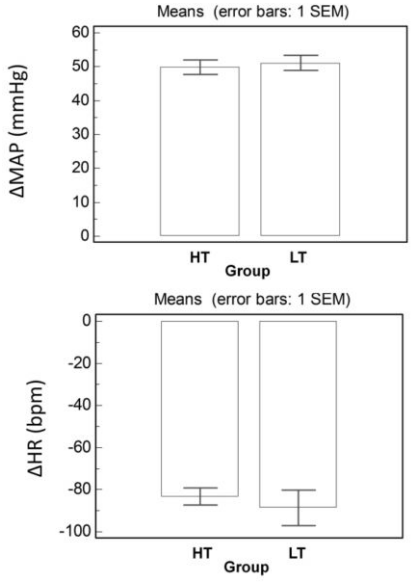

Figure 5. Increase in mean arterial pressure (MAP, mmHg) and decrease in heart rate (HR, bpm) in response to phenylephrine (PHE, 8 µg/kg i.v.) in the HT (n=18) and the LT groups (n=15).

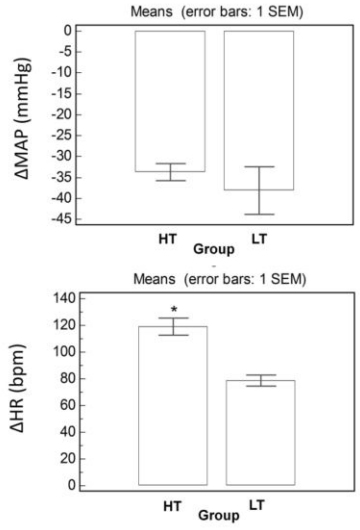

Figure 7. Decrease in mean arterial pressure (MAP, mmHg) and decrease in heart rate (HR, bpm) in response to sodium nitroprusside (SNP, 50µg/kg i.v.) in the HT (n=18) and the LT groups (n=15). *P<0.001: difference to the LT group.

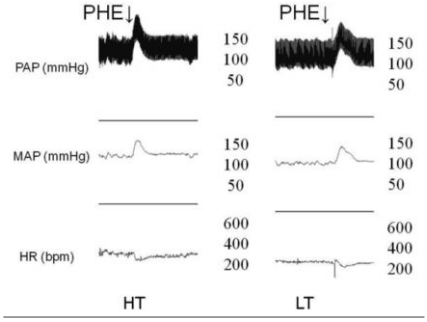

Figure 6. Recordings from one rat from the HT group and one from the LT group showing reflex bradycardia (top) in response to increases in blood pressure. Infusions were given in bolus. MAP, mean arterial pressure; PAP, pulsatile arterial pressure; HR, heart rate; PHE, phenylephrine.

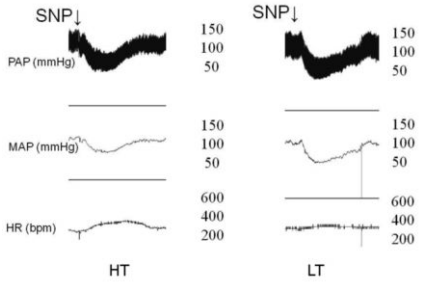

Figure 8. Recordings from one rat from the HT group and one from the LT group showing reflex tachycardia (top) in response to decreases in blood pressure. Infusions were given in bolus. MAP, mean arterial pressure; PAP, pulsatile arterial pressure; HR, heart rate; SNP, sodium nitroprusside.

determination was always obtained with the same dose of PHE and SNP. The range of mean blood pressure changes differed in some cases as shown in Figure 2. This means that different gains could have been obtained. Nonetheless, we believe that the fact that in our study the same drug concentration was used provides reliable information regarding baroreflex responses, rather than determining baroreflex gain according to variations in mean blood pressure, since differences in the drug concentration infused may influence autonomic responses.[24,25]

These data provide useful information given that currently many types of animals are widely studied in order to develop new therapies for the prevention of several cardiovascular disorders in humans.[9,27-34]

In conclusion, there was significantly reduced baroreflex function among Wistar rats. A large number of the animals presented attenuated parasympathetic activity of the baroreflex while approximately half presented decreased sympathetic activity of the baroreflex. This information is useful for researchers using Wistar rats in the laboratory and may help ensure that this strain is correctly used.

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