Treatment by N-Acetylcysteine and Melatonin Increases Cardiac Baroreflex and Improves Antioxidant Reserve

Hélène Girouard, Catherine Denault, Chantal Chulak, and Jacques de Champlain

Background: The aims of this study were to investigate the effects of melatonin and N-acetylcysteine on the baroreflex sensitivity and to verify whether those effects were correlated with their antioxidant capacity in Wistar-Kyoto and spontaneously hypertensive rats (SHR).

Methods: Rats were treated with 30 mg/kg/day of melatonin or 4 g/kg/day of N-acetylcysteine for 4 weeks. Changes in mean arterial pressure, heart rate, plasma norepinephrine, and epinephrine were measured in conscious rats after an intravenous injection of phenylephrine or sodium nitroprusside.

Results: The SHR were characterized by decreased reflex chronotropic responses to phenylephrine and sodium nitroprusside ($P < .001$ and $P < .001$), as well as by an enhanced increase in plasma catecholamine concentrations in response to sodium nitroprusside ($P < .001$). Melatonin and N-acetylcysteine produced a significant reduction in mean arterial pressure and heart rate in SHR ($P < .001$). Melatonin and N-acetylcysteine improved bradycardic ($P < .001$) and tachycardic ($P < .001$) baroreflex responses in SHR without modifying catecholamine responses. The antioxidant reserve, which was reduced in SHR as reflected by the lower glutathione peroxidase activity in plasma ($P < .05$), was normalized by N-acetylcysteine and melatonin ($P < .05$). N-acetylcysteine ($P < .001$) and melatonin ($P < .05$) increased glutathione peroxidase activity in erythrocytes from SHR.

Conclusions: The results of the present study suggest that melatonin and n-acetylcysteine improve the baroreflex response in SHR in correlation with the antioxidant effects of these substances. Am J Hypertens 2004;17:947–954

Key Words: Antioxidant, baroreflex, spontaneously hypertensive rat, superoxide dismutase, glutathione peroxidase, superoxide anion.

The modulation of arterial pressure by baroreflexes constitutes a fundamental mechanism whereby the central nervous system influences the regulation of the cardiovascular system. Dysfunctions in heart rate (HR) control have been demonstrated in essential hypertension,[1] genetic models of hypertension,[2,3] as well as various experimentally induced models of hypertension.[4,5] It has been postulated that abnormalities at various levels of the baroreflex arc could lead to a sympathetic hyperreactivity and thus to hypertension. In addition, it has been demonstrated that baroreflex sensitivity can predict the end-organ damage in hypertension[6] and can be associated with cardiac arrhythmias and sudden death in hypertensive patients.[7] Based on this consideration, it was proposed that an antihypertensive drug that could improve baroreflex sensitivity would offer additional benefit in the treatment of hypertension.

Arterial baroreceptors are constituted by mechanosensitive nerve endings localized in the arterial wall of the carotid sinus and could be activated by a vascular stretch during an increase in blood pressure (BP). However, the sensitivity of arterial baroreflexes is also determined by many neurohumoral substances as well as by paracrine agents such as free radicals. Moreover, it has been shown that an acute exposure of isolated carotid sinus to superoxide dismutase (SOD) and catalase increases the baroreceptor activity in atherosclerotic rabbit without any effects on normal rabbits.[8] In normal rabbits, exogenous free radicals produced by xanthine-xanthine oxidase (X-XO) were found to inhibit the baroreceptor activity in a revers-

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From the Research Group on Autonomic Nervous System, Department of Physiology, Faculty of Medicine, University of Montréal, Montréal, Québec, Canada.

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Address correspondence and reprint requests to Dr. Jacques de Champlain, Department of Physiology, Faculty of Medicine, Université de Montréal, C.P. 6128, Succ. Centre-ville, Montréal, Québec, Canada, H3C 3J7; e-mail: grsna@ere.umontreal.ca

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ible and dose-dependent manner.[8] In addition, the acute induction of a hyperglycemia was demonstrated to attenuate the baroreflex sensitivity in both healthy and type 2 diabetic patients through a glutathione sensitive mechanism that could be reversed by an infusion of L-arginine.[9,10]

Spontaneously hypertensive rats (SHR) are characterized by elevated oxidative stress,[11–14] and there is considerable evidence that the baroreflex control of HR is reduced in this model of hypertension.[2] Therefore, in this study, we postulated that baroreflex dysfunctions in SHR may be due to increased oxidative stress and consequently that the treatment with antioxidants could improve the baroreflex sensitivity in SHR. The present study was thus designed to evaluate the effect of chronic treatments with N-acetylcysteine (NAC) and melatonin on baroreflex control of HR and on the reflexively induced responses of plasma norepinephrine (NE) and epinephrine levels to the hypotension induced by sodium nitroprusside (SNP). The antioxidant potencies of NAC and melatonin were also evaluated in regard to the antioxidant reserve in the plasma and erythrocytes. Melatonin and NAC were chosen because they both are powerful antioxidants and possess broad antioxidant spectra. The compound NAC also contains thiol and can directly modify the redox status of thiol-containing proteins. In addition, melatonin can act through its receptors independently of its antioxidant effects.

Methods

Animals and Treatment

Male SHR and normotensive Wistar-Kyoto (WKY) rats, 11 weeks old, were obtained from Harlan Laboratories (Indianapolis, IN). The rats were treated and maintained in accordance with Canadian Council on Animal Care guidelines, and the study was approved by the local Institutional Animal Ethics Committee. The rats were housed under conditions of constant temperature and humidity and exposed to a 12-h light-dark cycle, with free access to standard laboratory rat chow (Basal Purified Diet 5755C; Purina Mills, St. Louis, MO) and drinking water. After a few days of acclimatization, rats were randomly divided into three groups: 1) untreated control group; 2) melatonin-treated group (30 mg/kg of body weight/day); and 3) NAC-treated group (4 g/kg of body weight/day). Fresh melatonin or NAC preparation was added to the drinking water each day at 6 pm for 4 weeks. Preliminary long term experiments showed that 30 mg/kg body weight/day of melatonin and 4 g/kg body weight/day of NAC for 4 weeks are the most effective doses and duration of treatment to obtain a decrease in both diastolic and systolic BP. Higher doses of NAC decreased the water intake and higher doses of melatonin required the use of ethanol as solvent so that the vehicle itself could influence BP.

Determination of BP and Heart Rate

Mean arterial pressure (MAP) and HR were measured in chronically cannulated conscious and unrestrained animals under resting conditions. After 4 weeks of melatonin or NAC treatment, rats were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally, with supplemental doses of 25 mg/kg intraperitoneally administered as needed), and the femoral artery and vein were cannulated with polyethylene tubing (PE-10) welded to PE-50 catheters. Both catheters were positioned in the abdominal aorta and vena cava, tunneled subcutaneously, extruded at the back of the neck, and protected from the rat by insertion into a stainless steel tether. The catheters were filled with heparinized saline and the rats were placed in individual cages, where they were allowed to recover for at least 24 h. The arterial catheter was coupled to a pressure transducer (Statham P231D, Gould Statham Inc., Hatorey, Puerto Rico), and the signal was amplified and recorded by a Biopac data-acquisition system (MP100WS, Harvard Apparatus Canada). The MAP and HR were monitored with a computerized analysis program (Acknowledge 3.0, Harvard Apparatus, South Natick, MA). When MAP had reached stable basal levels, after at least 20 min of continuous recording, basal values were measured. At the end of the baseline period, a bolus injection of phenylephrine (PHE; 1 to 20 mg/kg) was administered in a noncumulative manner or SNP (50 μg/kg) was infused during 5 min through the left femoral venous catheter. The changes in HR evoked by injections of PHE and SNP reflect the peak changes in HR averaged for 1 sec for each PHE concentration and every 5 sec during the BP decrease after SNP infusion. The BP decrease after SNP infusion lasted 25 sec.

Determination of Plasma Catecholamine Level

Aortic blood samples (0.4 mL) were taken at the end of the treatment period at 8:00 AM, 24 h after the surgery in chronically cannulated conscious rats, and were placed in ice-chilled tubes containing a preservative solution (0.25 EGTA and 0.2 mol/L reduced glutathione, pH7). The samples were rapidly centrifuged at 14,000 *g* for 5 min at 4°C. The plasma was frozen at −80°C until the assay. Plasma NE and epinephrine concentrations were measured by HPLC as previously described.[15]

Glutathione Peroxidase and Superoxide Dismutase Assays

Aortic blood samples (0.5 mL for superoxide dismutase [SOD] and 1 mL for glutathione peroxidase [GPX]) taken at the end of the treatment period at 8 AM, 48 and 72 h after the surgery, in chronically cannulated conscious rats and were placed in ice-chilled tubes containing heparin. The surgery did not have any effect on SOD and GPX activity. The samples were rapidly centrifuged at 1000 *g* for 10 min

at 4°C. Erythrocytes were washed (twice for GPX and four times for SOD) in 0.9% saline solution, centrifuged, and kept at 4°C for the lysis of cells. After dilution with 0.01 mol/L phosphate buffer pH 6.6, the plasma and erythrocytes were frozen at −80°C until the assay. Erythrocytes and plasma SOD activity was determined spectrophotometrically using a kit from Randox Laboratories Canada Ltd. (Mississauga, ON, Canada). The GPX activity in erythrocytes and plasma was evaluated as previously described.[16]

Statistical Analysis

Values are given as the mean ±SEM, with *n* indicating the number of observations. Statistical analysis was performed using the analysis of variance (two-way or one-way ANOVA) followed by a Bonferroni multiple comparison analysis when *F* values were significant. Linear regression analysis was used to evaluate cardiac baroreflex function. The analysis of the data for cardiac baroreflex was performed from each individual animal and the slopes presented the mean of the pressure-HR relations. All statistical analysis was performed using the program GraphPad Prism for Windows, version 2.01 (GraphPad Inc., San Diego, CA). Statistical significance was considered at $P < .05$.

Drugs

All drugs and chemical components of solutions were purchased from Sigma Chemical Co. (St. Louis, MO).

Determination of Heart Weight

At the end of the study period, rats were killed and the right and left ventricles as well as the septum were excised and weighed.

Results

Effects of N-acetylcysteine or Melatonin Treatment on BP, Heart Rate, Myocardial Hypertrophy, and Catecholamine Levels

Both MAP and HR measured in chronically cannulated conscious rats were significantly higher in 15-week-old SHR compared with age-matched WKY rats (Table 1). A 4-week period of treatment with melatonin or NAC in SHR reduced MAP by 21 mm Hg and HR by 33 beats/min and 51 beats/min, respectively. Administration of melatonin or NAC had no significant effect on these parameters in WKY rats (Table 1). Hearts from SHR demonstrated left ventricular hypertrophy, which was attenuated by NAC therapy whereas the antihypertensive effect of melatonin was not accompanied by a reduction of left ventricular relative weight in SHR (Table 1). Plasma NE levels were higher in untreated SHR compared with WKY rats, whereas plasma epinephrine levels, although slightly higher in SHR, did not differ significantly (Table 1). Mel-

Table 1. Hemodynamic parameters and cardiac weights in control and melatonin or N-acetylcysteine–treated Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR)

Group	WKYCTL	WKYMEL	WKYNAC	SHRCTL	SHRMEL	SHRNAC
MAP (mm Hg)	103 ± 3	107 ± 4	103 ± 2	152 ± 2*	131 ± 5*†	131 ± 5*†
Heart rate (beats/min)	314 ± 24	329 ± 8	326 ± 4	380 ± 6‡	347 ± 7§¶	329 ± 12§
Plasma NE (pg/mL)	122 ± 7	86 ± 12	82 ± 17	176 ± 21‡	112 ± 17‖	74 ± 3†
Plasma E (pg/mL)	38.7 ± 4.9	42.2 ± 11.5	47.8 ± 9.9	63.3 ± 17.6	36.3 ± 14.0	53.2 ± 23.1
BW (g)	315 ± 8	321 ± 5	306 ± 7	347 ± 5‡	340 ± 3¶	319 ± 4
LVW/BW (mg/g)	1.83 ± 0.03	1.87 ± 0.06	1.75 ± 0.09	2.01 ± 0.03¶	2.02 ± 0.04¶	1.80 ± 0.08§
RVW/BW (mg/g)	0.68 ± 0.04	0.70 ± 0.07	0.62 ± 0.07	0.68 ± 0.03	0.68 ± 0.07	0.65 ± 0.03

BW = body weight; CTL = control; E = epinephrine; LVW = left ventricular weight; MAP = mean arterial pressure; MEL = melatonin-treated rats; NAC = N-acetylcysteine–treated rats; NE = norepinephrine; RVW = right ventricular weight.
Values are mean ± SEM, $n = 6–11$.
* $P < .001$, SHR *v* WKY; † $P < .001$, treated *v* untreated; ‡ $P < .01$, SHR *v* WKY; § $P < .05$, treated *v* untreated; ¶ $P < .05$, SHR *v* WKY; ‖ $P < .01$, treated *v* untreated.

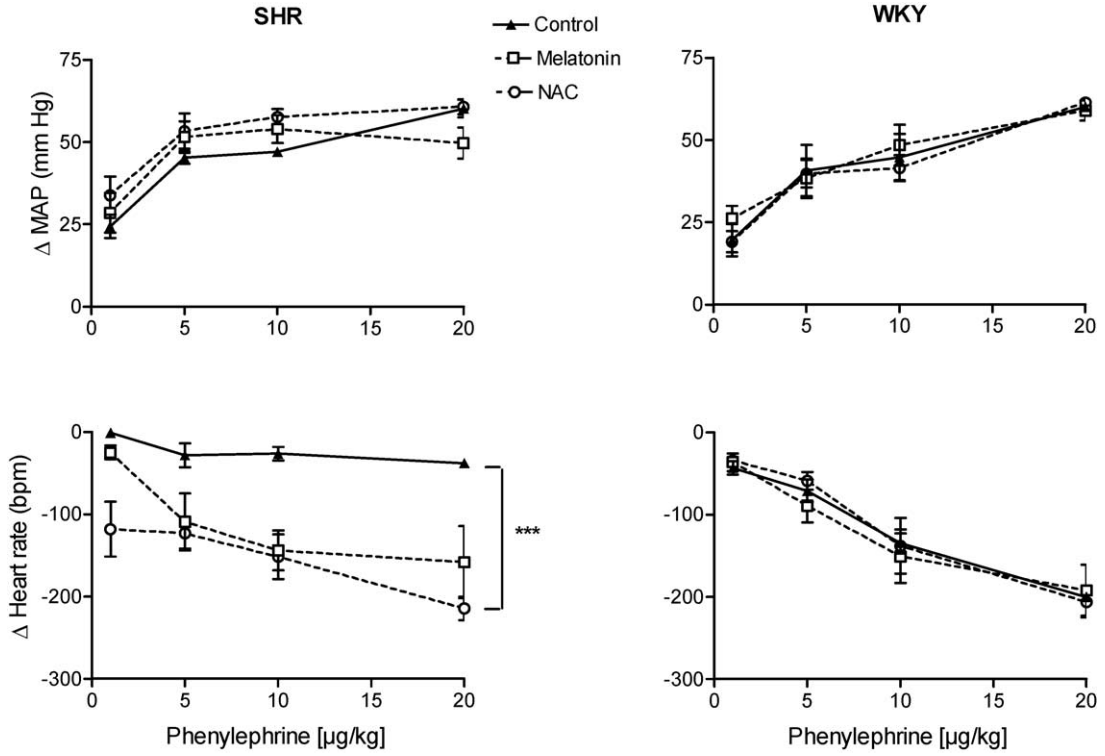

FIG. 1. Changes in mean arterial pressure (Δ MAP) (**upper panels**) and heart rate (Δ Heart rate, in beats/min [bpm]) (**lower panels**) in spontaneously hypertensive rats (SHR) (**left panels**) and Wistar-Kyoto (WKY) rats (**right panels**) measured after five bolus injections of phenylephrine at increasing concentrations (1, 5, 10, and 20 μg/kg intravenously) in control (▲), melatonin-treated (□), and n-acetylcysteine (NAC)-treated (o) SHR and WKY rats. Data are expressed as mean ± SEM; $n = 6$ to 8. ***$P < .001$ treated versus untreated rats.

atonin or NAC treatment significantly decreased plasma NE level in SHR and WKY rats. Both treatments had no significant effects on epinephrine levels in either group of rats (Table 1).

Effect of N-acetylcysteine or Melatonin Treatment on Baroreflex

The rise in BP induced by bolus administrations of increasing concentrations of PHE (1, 5, 10, and 20 μg/kg intravenously) did not differ in treated and untreated SHR and WKY rats (Fig. 1). The HR response to PHE was significantly blunted in untreated SHR compared with WKY rats and the chronic treatments with either NAC or melatonin improved the HR response in SHR exclusively (Fig. 1).

Hypotension induced by the 5-min infusion of SNP was similar in treated and untreated SHR and WKY rats (Fig. 2). The response to SNP-induced hypotension was characterized by an increase in HR that was significantly smaller in SHR than in WKY rats ($P < .001$). Long term treatment with NAC or melatonin improved the HR response in SHR only (Fig. 2). The increases in plasma NE and epinephrine in response to the decrease in MAP induced by SNP were higher in untreated and treated SHR than in WKY rats, suggesting enhanced sympatho-adrenal reactivity in those hypertensive animals. The NAC or melatonin treatments did not modify the increases in either amines after hypotension (Fig. 3). These results demonstrate that the potentiation of the HR in response to SNP infusion by NAC and melatonin treatments in SHR was not associated with a concomitant change in sympatho-adrenal reactivity, as reflected by the absence of change in plasma NE and epinephrine responses (Figs. 2 and 3).

Baroreflex control of the HR was assessed by linear regression analysis of the changes in HR in response to changes in MAP induced by infusion of SNP and PHE (Fig. 4). The baroreflex control of the HR, which was blunted in SHR compared with WKY ($P < .001$), was improved and sensitized by treatments with NAC or melatonin in SHR only (Fig. 4).

Effect of N-acetylcysteine or Melatonin on Antioxidant Reserve

Both GPX and SOD activity were measured in plasma and erythrocytes from treated and untreated SHR and WKY rats, as depicted in Fig. 5. We found that GPX activity was lower in plasma from SHR than from WKY rats, whereas it was similar in erythrocytes. Chronic NAC or melatonin treatments increased the GPX activity in erythrocytes and plasma from SHR. In contrast, SOD activity was higher in plasma and erythrocytes from SHR than from WKY rats. Melatonin or NAC treatments did not have any effect on SOD activity.

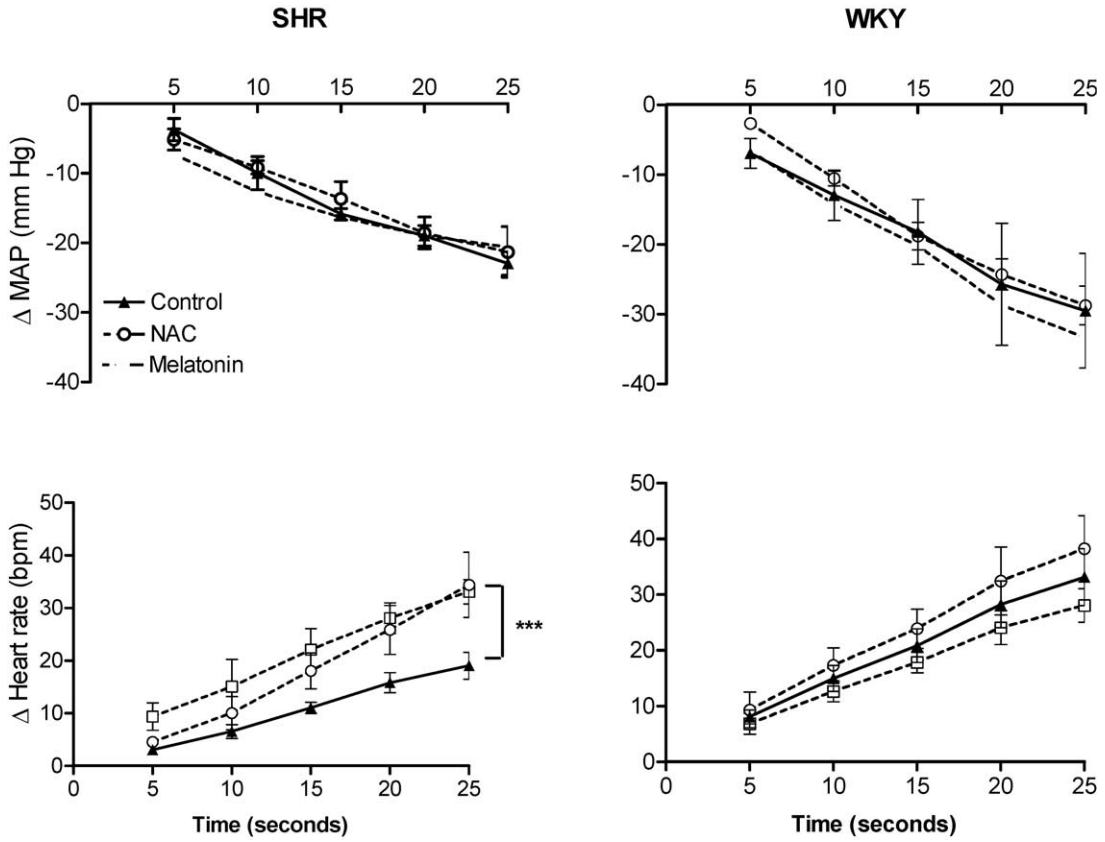

FIG. 2. Changes in mean arterial pressure (Δ MAP) (**upper panel**) and heart rate (Δ Heart rate) (**lower panel**) induced by infusion of sodium nitroprusside (5 min) measured every 5 sec during the decrease in blood pressure in control (▲), melatonin-treated (□), and NAC-treated (o) SHR and WKY rats. Data are expressed as mean ± SEM; $n = 4$ (control), $n = 5$ (melatonin-treated), and $n = 6$ (NAC-treated) rats. ***$P < .001$ treated versus untreated rats. Abbreviations as in Fig. 1.

Discussion

The major findings of this study are as follows: 1) long term NAC or melatonin treatment decreased the MAP and HR in SHR; 2) NAC or melatonin treatment improved baroreflex control of HR in response to pressor and depressor stimulations in SHR; 3) NAC or melatonin treatments decreased basal plasma NE levels in SHR; 4) improved baroreflex sensitivity after chronic NAC or melatonin treatments was not accompanied by changes in the pressure-induced sympatho-adrenal reactivity; 5) only NAC treatment and not melatonin treatment attenuated cardiac hypertrophy in SHR; and 6) NAC or melatonin were found to improve GPX activity in plasma and erythrocytes of SHR.

The present study showed that the bradycardic response to PHE and the tachycardic response to SNP were attenuated in SHR. The linear regression analysis of the reflex changes in HR in response to changes in MAP indicated a decreased baroreflex sensitivity in SHR compared with WKY rats. Moreover, the hypotension induced by SNP was associated with potentiated increases in NE and epinephrine levels in SHR compared with WKY rats, suggesting a sympathoadrenal hyperreactivity in that model of hypertension, as previously reported.[17] These results suggest that the baroreflex impairment in SHR does not result from a decrease in peripheral sympathetic output. Head and Adams[2] have also suggested that the differences in baroreflex control of HR between SHR and WKY may be related to a difference in the sensitivity of the vagus cardiac effector. The lower increase in HR during SNP-induced hypotension despite an increase in catecholamine levels may also be attributed to the decrease in β-adrenergic receptor number and sensitivity in the heart from SHR.[18]

The chronic NAC or melatonin treatments improved the baroreflex sensitivity in SHR to depressor and pressor responses to SNP and PHE, respectively. However, long term treatment with NAC and melatonin did not attenuate the reflexively induced increase in catecholamine levels, although they decreased the basal NE levels. This suggests a specific inhibitory effect of these antioxidants on sympathetic nerves without altering the adrenal medullary activity. Indeed, it has been reported that the atrial field-stimulated release of NE was decreased in SHR concomitantly to a reduction in MAP and HR after chronic antioxidant treatments.[18] This inhibitory effect of NAC and melatonin on basal NE levels could favor the vagal baroreflex component in SHR. However, this does not

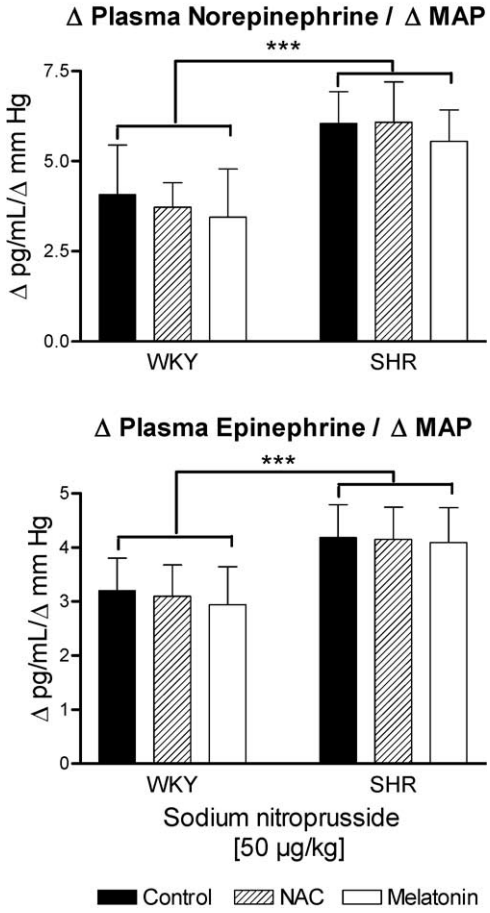

FIG. 3. Increases in plasma norepinephrine (**upper panel**) and epinephrine (**lower panel**) over decreases in blood pressure induced by infusion of nitroprusside (5 min) in untreated (control), melatonin-treated, and NAC-treated WKY rats and SHR. Data are mean ± SEM; $n = 4$ to 10. ***$P < .01$ SHR versus WKY rats. Abbreviations as in Table 1.

exclude the possibility of an improvement in the β-adrenergic receptor sensitivity in the heart from SHR by NAC or melatonin treatments.[18] Moreover, the decreased sympathetic basal activity induced by melatonin or NAC treatments could participate in the lowering of BP and HR, which may contribute to the improved baroreflex sensitivity.

However, the cardiac baroreflex, but not the BP, was restored to normal by NAC or melatonin treatments, suggesting that the reflex sensitivity could be partly modulated by some specific actions of NAC and melatonin on that central nervous system in addition to the reduction in arterial pressure. Furthermore, it was shown that in terms of arterial pressure reduction, there are no large differences among the major classes of antihypertensive agents (that is, diuretics, β-blockers, α_1-blockers, calcium channel antagonists, and angiotensin-converting enzyme inhibitors); however, they are known to have variable effects on the sympathetic nervous system and baroreflex mechanisms. Kumagai et al[19] studied the effects of different antihypertensive agents such as trichlormethiazide (diuretic), atenolol (β-blocker), nicardipine (calcium channel blocker), and enalapril (angiotensin-converting enzyme inhibitor) on the baroreflex sensitivity in SHR. In that study, the antihypertensive treatments reduced the MAP by about 20 mm Hg but had variable effects on the sensitivity of the baroreflex. In fact, reflex tachycardia was increased in trichlormethiazide, nicardipine and enalapril-treated SHR but not in atenolol-treated SHR, whereas reflex bradycardia was increased in atenolol-treated SHR only. In the present study, NAC and melatonin reduced MAP by 21 mm Hg and restored both reflex tachycardia and bradycardia.

It has been proposed that prevention of cardiac hyper-

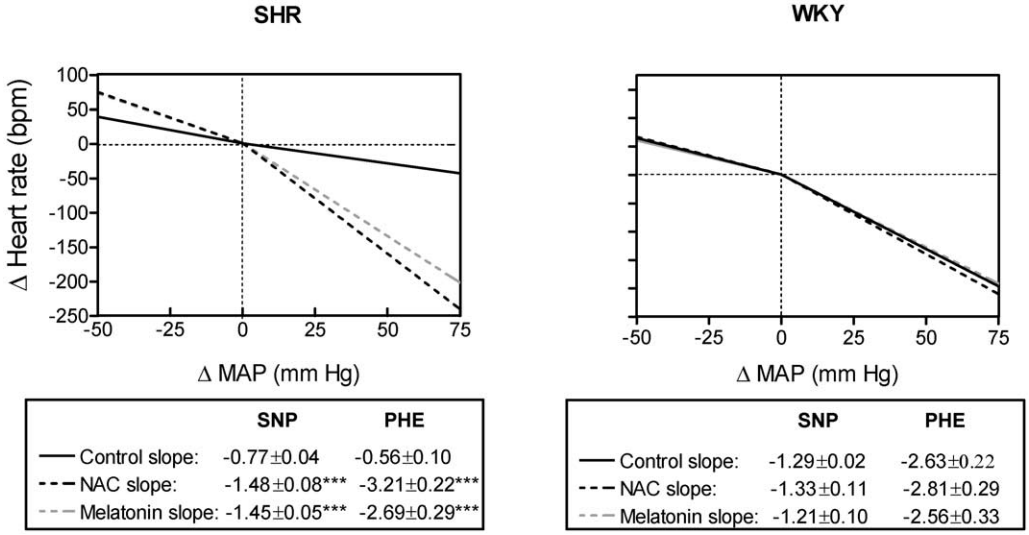

FIG. 4. Reflex bradycardia in response to bolus administrations of increasing concentrations of phenylephrine (PHE; 1, 5, 10, and 20 μg/kg intravenously) and reflex tachycardia in response to infusion of nitroprusside (SNP; 5 min) measured every 5 sec during the decrease in blood pressure (BP) in SHR (**left panel**) and WKY rats (**right panel**) in control, melatonin-treated, and NAC-treated rats. Peak changes in HR (Δ Heart rate) for each change in BP (Δ MAP) are plotted. Linear regression analysis for the slope of the response (Δ Heart rate/ΔMAP) is shown. Data are mean ± SEM; $n = 4$ to 8: ***$P < .001$ treated versus untreated rats.

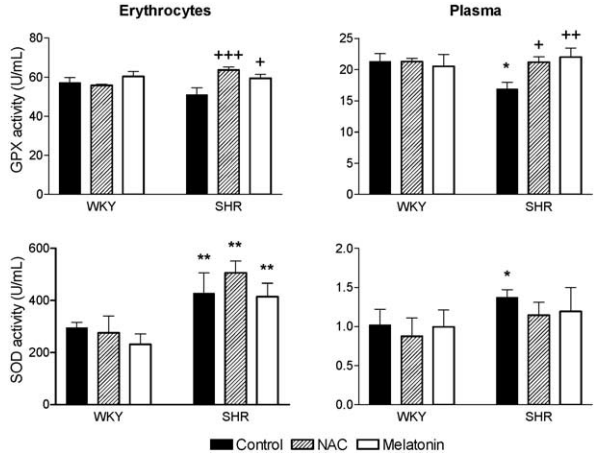

FIG. 5. Glutathione peroxidase (GPX) (**upper panels**) and superoxide dismutase (SOD) (**lower panels**) activity in erythrocytes (**left panels**) and plasma (**right panels**) from WKY rats and SHR untreated (control) and melatonin-treated or NAC-treated animals. Data are mean ± SEM; $n = 4$ to 10. $*P < .05$, $**P < .01$ in SHR versus WKY rats; and $+P < .05$, $++P < .01$, and $+++P < .001$ in treated versus untreated rats.

trophy could be the major requirement for normalizing the vagal component of the baroreceptor-HR reflex in SHR.[20] Structural changes were estimated to account for only two thirds of the vagal deficit, with the remainder being related to the renin-angiotensin system.[20] In the present study, the fact that only NAC treatment decreased cardiac hypertrophy in SHR may explain the stronger but nonsignificant effect of NAC over melatonin on the improvement of the baroreflex sensitivity. This effect of NAC on cardiac hypertrophy has also been observed in angiotensin II-induced[21] and mechanical stress-induced[22] cardiac hypertrophy, but no effect of melatonin on cardiac hypertrophy has been reported. The effect of NAC on cellular progression and proliferation has been attributed to the combined presence of the thiol and amines groups,[23] which affect the reduction/oxidation processes as well as the polyamine-related processes, respectively.

Both NAC and melatonin are known to be powerful and nonspecific antioxidants. This may explain their beneficial effects on the baroreflex sensitivity of SHR, as decreased baroreflex sensitivity has been correlated with oxidative stress.[8–10] Furthermore, the treatment with angiotensin was also found to attenuate the baroreflex sensitivity[24] while simultaneously stimulating superoxide anion production through activation of the membrane-bound NADH/NADPH system.[25,26] The increased superoxide anion production in vessels from SHR was also attributed to an increased NAD/NADPH oxidase activity.[15,26] Thus, the improved baroreflex sensitivity by NAC or melatonin may be in great part related to the reduction in oxidative stress in the periphery or central nervous system of SHR. An alteration of the afferences from baroreceptors affects both sympathetic and vagus efferent pathways. Because the effect of NAC and melatonin on cardiac baroreflex is not mediated by a decrease in the sympathetic reflex response, this suggests that these antioxidants act in the central nervous system or the cardiac vagal efferent. According to the literature, there are at least two potential mechanisms whereby the antioxidant potential of NAC and melatonin may improve baroreflex. The first is by increasing the bioavailability of NO in the brainstem, especially in the nucleus ambiguous,[27] whereas NO activates cardio-inhibitory sites and thus decreases HR. The second is by scavenging the free radicals induced by angiotensin in the dorsomedial nucleus solitary tract at the level of the area postrema,[28] whereas it produces a losartan-sensitive attenuation of the cardiac vagal component of the baroreflex.[29]

In the present study, long term treatment with NAC or melatonin increased the antioxidant reserve by normalizing the reduced GPX activity in SHR. In addition, Cabassi et al[12,13] have shown an increase in plasma melondialdehyde (MDA), an index of tissue lipid peroxidation, and an increase of oxidized/reduced glutathione balance (GSSG/GSH), an index of oxidized thiols, in SHR. The use of chronic NAC or melatonin treatments at the same concentrations as those used in the present study was found to normalize plasma MDA and of GSSG/GSH in SHR. These results suggest that the doses of melatonin and NAC used in the present study are sufficient to increase the antioxidant reserve resulting in a decrease in cell damages such as the membrane peroxidation and oxidation of thiols which were observed in SHR.

In conclusion, our data support the existence of impaired baroreflex sensitivity and of hypereactivity of the sympathetic nervous system in the pathogenesis of hypertension in SHR. However, the reactivity of plasma catecholamine levels in response to changes in MAP does not correlate with the reduced cardiac baroreflex in SHR, suggesting the participation of a reduced vagal sensitivity or a reduced β-adrenergic sensitivity instead of a reflex sympathetic deficit in this phenomenon. Long term treatment with NAC or melatonin normalized cardiac baroreflex in SHR and decreased the basal NE release without modifying the reflex response of the sympatho-adrenal system, suggesting an improved vagal sensitivity or an improved β-adrenergic sensitivity, or both. Moreover, observations from our laboratory support the presence of an increased oxidative stress in SHR and suggest that the free radical-scavenging properties of NAC and melatonin, as well as their capacity to improve the antioxidant reserve, may have contributed to their beneficial effects on the baroreflex sensitivity in SHR. However, the lowering of BP and HR may also contribute to the improved baroreflex sensitivity. Although the importance of antioxidants on cardiac baroreflex remains to be examined in a future study using shorter antioxidant treatments; nonetheless, those results suggest that antioxidants may be beneficial in the management and correction of cardiac baroreflex dysfunction related to hypertension.

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