Early Depression of the Baroreceptor Sensitivity During Onset of Hypertension


We studied the correlation of changes in gain sensitivity of the baroreceptors and the development of resetting of the baroreceptors 2 and 6 days after the onset of hypertension produced by subdiaphragmatic aortic constriction in rats. Mean arterial pressure of anesthetized rats was maintained at approximately the same level as that of conscious rats, and baroreceptor function curves were studied on a beat-to-beat basis by computer. After 2 days of hypertension, the difference between the systolic pressure threshold and the control diastolic pressure was 13 ± 2 mm Hg (125 ± 3 versus 138 ± 4 mm Hg). Individual values showed that in seven of nine hypertensive rats, the difference was less than 15 mm Hg, indicating complete resetting. After 6 days of hypertension, all rats exhibited complete resetting, when the systolic pressure threshold was similar to control diastolic pressure (143 ± 4 versus 141 ± 2 mm Hg), indicating that more than 2 days of hypertension is necessary for full displacement of the pressure thresholds when all hypertensive rats are considered. Slopes of the baroreceptor curves after 2 and 6 days of hypertension showed that baroreceptor gain was depressed by 25% and 34%, respectively. The difference was not statistically significant (1.07 ± 0.054% versus 0.94 ± 0.049% and 1.43 ± 0.075% in controls). When changes in pressure were circumscribed to a more physiological range, a depression of 25% in response to +10 mm Hg and 37% in response to −10 mm Hg was observed. The data indicate that a depression of the baroreceptor gain, similar to that observed previously after 2 months of hypertension, is already present after only 2–6 days of hypertension, when complete resetting is also detected. (Hypertension 1992;19[suppl. II]:II-198–II-201)
the present experiments were undertaken to study 1) the gain sensitivity of the baroreceptors in rats with hypertension (subdiaphragmatic aortic constriction) of 2 and 6 days' duration, and 2) the extent of resetting after 2 and 6 days of hypertension.

Methods
Male Wistar rats weighing 200–250 g were used. The procedure for recording whole nerve activity of the aortic baroreceptors in rats anesthetized by pentobarbital sodium anesthesia (40 mg/kg) was similar to that used in previous studies. Aortic fibers of the left isolated aortic nerve or as a branch isolated from the left recurrent laryngeal nerve in the lower part of the neck were used. To assure the stability of the neural recording, a flexible thin 0.5-cm gold electrode (0.05 mm diameter) connected to a 10-cm platinum wire (0.05 mm diameter) covered by a vinyl tube (0.50×0.20 mm) was placed around the nerve and carefully insulated with silicone rubber (Wacker Sil-Gel 604, Wacker Co., Munich, FRG). The pressure threshold at which the aortic baroreceptors initiated firing and the pressure–nerve activity relation from low to high pressure levels were measured during rapid (10–15 seconds) changes of pressure produced by withdrawal and infusion of blood into the femoral artery. To avoid the influence of hypnosis, we used only the values obtained when pressure was changed from low to high levels to build the baroreceptor function curves. Arterial pressure (carotid artery) and aortic baroreceptor activity were continuously monitored on an oscilloscope (5115 Storage Oscilloscope, Tektronix, London) and recorded on a tape recorder (model 3960, Hewlett-Packard Co., Atlanta, Ga.) for analysis. The data presented are the average of two to three consistent measurements made during each experimental situation. To quantify the whole nerve activity, the nerve traffic was amplified, full wave rectified, and integrated with a time constant of 3.9 msec. The integrator output provides the nerve activities for each pulse pressure, which permits the study of the pressure–nerve activity relation on a beat-to-beat basis by computer (model PC-XT, Itautec, Sao Paulo, Brazil) with a 10-bit analog-to-digital converter (model CAD 1016, Lynx, Sao Paulo, Brazil) and a 120-Hz sample rate.

Direct arterial pressure was measured in freely moving rats by means of a plastic cannula inserted into the carotid artery with rats under ether anesthesia 1 day before the acute experiment. The cannula emerged through the back of the rat and was connected to a strain-gauge transducer (Statham P23 Db) from which the signals were fed into a multichannel recorder (model 7754A, Hewlett-Packard). The anesthesia level was adjusted to maintain the arterial pressure at the same level existing in conscious rats before the first baroreceptor function curve was recorded during the control period. Sustained arterial hypertension in the upper part of the systemic circulation was produced by narrowing the aorta just below the diaphragm according to the technique of Beznak as modified by Krieger. Briefly, median laparotomy was performed with rats under ether anesthesia, and the abdominal aorta was isolated. A cotton thread was used to constrict the aorta; the extent of narrowing was limited by a hypodermic needle 0.7 mm in diameter. The level of hypertension was measured in conscious, undisturbed rats before anesthetization to record the baroreceptor function.

Results are presented as mean±SEM. Differences in PA values for activation of the baroreceptors were calculated by using one-sample profile analysis, and the displacement of the slope of the baroreceptor function curves was calculated by using regression analysis. Differences were considered significant at values of p<0.05.

Resetting of the Baroreceptors
The anesthesia level was adjusted to maintain the arterial pressure at the same level existing in conscious rats before the baroreceptor function curves were recorded (107±2 versus 104±3 mm Hg in controls, 154±5 versus 150±3 and 160±3 versus 161±3 mm Hg of mean arterial pressure, respectively, 2 and 6 days after aortic constriction). Heart rate was similar in the three groups: 367±15, 375±22, and 381±13 beats per minute, respectively. In normotensive rats, the systolic pressure threshold (SPa) that initiates baroreceptor firing is approximately equal to the control diastolic pressure (CDP). Moreover, complete resetting, when pressure is constantly changed to hypertensive or hypotensive levels, occurs when baroreceptors again begin to fire at a SPa similar to the new CDP. With this criterion, seven of nine hypertensive rats had complete baroreceptor resetting after 2 days of aortic constriction, because the differences of SPa and CDP were less than −15 mm Hg (range of normality). The average difference of SPa and CDP for the entire group was −13.1±1.9 mm Hg (125±3 versus 138±4 mm Hg). After 6 days of hypertension, the 11 hypertensive rats exhibited complete resetting, the value of SPa (143±4 mm Hg) being similar to that of CDP (141±2 mm Hg). The average difference (+2.3±3.1 mm Hg) was approximately the same as that of control rats (+1.2±3.2 mm Hg). SPa and CDP values of control animals were 97±2 and 96±2 mm Hg, respectively.

Changes in Gain Sensitivity
The resetting of the baroreceptors (displacements of PA) was accompanied by a significant decrease of the baroreceptor gain when the entire baroreceptor pressure–activity curves were analyzed (Figure 1). The full range of systolic pressure for baroreceptor activation increased to 92 mm Hg (125±3 to 217±4 mm Hg) and 102 mm Hg (143±4 to 245±6 mm Hg), respectively, after 2 and 6 days of hypertension in comparison with the value of 72 mm Hg (97±2 to 169±5 mm Hg) in control rats. The slope decreased significantly from the present experiments were undertaken to study 1) the gain sensitivity of the baroreceptors in rats with hypertension (subdiaphragmatic aortic constriction) of 2 and 6 days' duration, and 2) the extent of resetting after 2 and 6 days of hypertension.

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Gain sensitivity of the baroreceptors was also analyzed in six rats with 2 days of hypertension when changes in pressure were circumscribed to a more physiological range (-10 and +10 mm Hg in the control pressure). Comparison of the actual values of the baroreceptor discharges in two hypertensive rats and one normotensive rat (Figure 2, top panel) illustrated the great depression in gain of the baroreceptors. For the entire group (Figure 2, bottom panel), the gain sensitivity was reduced by 25% in response to -10 mm Hg and by 37% in response to -10 mm Hg.

Discussion

After only 2 days of hypertension, most of the rats (seven of nine) in the present study had complete resetting of the baroreceptors to the new hypertensive levels. These results confirm previous observations7 that nine of 10 hypertensive rats exhibited complete resetting after the first 2 days of hypertension. After 6 days of hypertension in the present study, all rats had complete resetting. At that time, $S_{Pa}$ values for activation of the baroreceptor matched CDP values (143±4 versus 141±2 mm Hg), the same relation existing in the normotensive rats. This indicates that more than 2 days of hypertension is necessary for the full displacement of $P_{a}$ when all hypertensive rats are considered. However, one of the most important findings in this experiment is that, coincidental with the complete resetting present after 2 and 6 days of hypertension, a marked depression in the gain sensitivity of the baroreceptors was also observed when the entire baroreceptor function curves were analyzed on a beat-to-beat basis by computer. The decreased baroreceptor gain after 6 days was only slightly greater than after 2 days of hypertension, but the difference was not statistically significant. Moreover, the depression in gain observed previously in renal hypertensive rats with hypertension of 2 months' duration5 was only slightly higher than that observed presently after 6 days of hypertension (36% versus 32%). Thus, most of the impairment observed in chronic hypertension is already seen very early as soon as complete resetting occurs.

Another interesting observation is that the aortic pulsation recorded in freely moving rats after 2 days9 and 2 months10 of hypertension exhibited an almost identical increase: 0.051±0.005 and 0.058±0.006 mm, respectively, in comparison with 0.025±0.002 mm in normotensive rats. Because in both circumstances the baroreceptors are equally reset to operate at the hypertensive levels exhibited by the rats, approximately the same extent of decreased sensitiv-
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ity of the baroreceptors to strain should be postu-
lated, independent of the duration of hypertension. These findings taken together with the present ob-
servations support the concept that in hypertension the depression of the gain sensitivity appears simulta-
neously with complete resetting and remains relatively constant from 2–6 days up to 2 months of hyperten-
sion. As stressed in previous studies, the time course for the aortic caliber to achieve maximal dilation closely coincides with the time the barore-
ceptors take to complete the resetting process during the development of hypertension in rats with aortic constriction. It seems that complete resetting occurs when the increased pressure no longer effectively strains diastolic caliber, because the mechanoelastic properties of the wall have changed, allowing the vessel to dilate and to achieve a new diastolic resetting caliber. In this new state of equilibrium, the sustained elevated diastolic pressure no longer stim-
ulates the receptors that are distorted when the resting caliber is again momentarily distended by the pulse pressure. Finally, it is remarkable that the decreased gain sensitivity of the baroreceptors, which appears simultaneously with complete resetting after 2 days of hypertension, is of the same magnitude as that observed after 2 months of hypertension. In both circumstances, the aortic pulsation is twice that of control rats, the only difference being that dilation of the aorta is greater after 2 months (20%) than after 2 days (6.8%).

References

Key Words • baroreceptors • baroreceptor hypertension • baroreceptor reflex
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