Catecholamine-Related Gene Expression Correlates With Blood Pressures in SHR

Valin Reja, Ann K. Goodchild, Paul M. Pilowsky

Abstract—In this study we aimed to determine whether the levels of gene expression for phenylethanolamine-N-methyltransferase (PNMT), noradrenaline transporter (NAT), \(\alpha_{1A}-\) receptor (\(\alpha_{1A}-R\)), and \(\alpha_{2A}-\) receptor (\(\alpha_{2A}-R\)) vary with resting systolic blood pressure in spontaneously hypertensive rats (SHR) compared with normotensive Wistar-Kyoto (WKY) or Sprague-Dawley (SD) rats. Sites examined included central and peripheral regions associated with the control of arterial pressure. Twenty week old SD (\(n=6\)), WKY (\(n=6\)), and SHR (\(n=6\)) were used. Systolic blood pressure was measured using tail cuff plethysmography 2 weeks before tissue extraction. RNA was isolated and reverse-transcribed into cDNA. Gene expression levels were measured, using quantitative real time PCR, relative to the expression of GAPDH. PNMT, NAT, and \(\alpha_{1A}-R\) mRNA expression was significantly greater in SHR tissue samples compared with normotensives. In the rostral ventrolateral medulla, PNMT mRNA in SHR was 3 times greater than that in WKY (SHR: 0.82±0.02%; WKY: 0.29±0.02%). The amount of \(\alpha_{2A}-R\) mRNA was significantly lower in SHR compared with normotensives. For example, the level of \(\alpha_{2A}-R\) mRNA in spinal cord of SHR was 3 times less than that found in WKY (SHR: 1.85±0.04%; WKY: 3.26±0.07%). PNMT, NAT, and \(\alpha_{1A}-R\) mRNA levels were positively correlated with systolic blood pressure in all central tissue investigated. Conversely, \(\alpha_{2A}-R\) mRNA levels in central sites were negatively correlated with systolic blood pressure. Clearly, a decrease in central \(\alpha_{2A}-R\) and an increase in \(\alpha_{1A}-R\) is consistent with the elevated blood pressure and sympathetic activity observed in SHR. (Hypertension. 2002;40:691-697.)

Key Words: catecholamines ■ hypertension, genetic ■ receptors, adrenergic alpha ■ renin-angiotensin system ■ sympathetic nervous system.
activation closes voltage-gated Ca\(^{2+}\) channels and opens K\(^{+}\) channels.\(^7\) The \(\alpha_{2A}\)-R displays high immunoreactivity in the spinal cord and lower brain stem and is also expressed in some peripheral tissues, but in lower amounts.\(^7\) Catabolism and reuptake of noradrenaline within the synaptic cleft is achieved either by the actions of the catabolic enzymes catechol-O-methyltransferase\(^8\) and monoamine oxidase\(^8\) or by the noradrenaline transporter (NAT), which has been localized to regions of the pons and medulla oblongata.\(^9\) The aims of this study were, first, to measure the levels in expression of the genes for PNMT, NAT, \(\alpha_{2A}\)-R, and \(\alpha_{2C}\)-R in hypertensive rats and compare them with normotensive rats at central and peripheral tissue sites that are involved in the sympathetic control of arterial blood pressure. Secondly, our aim was to determine if any relationship exists between levels of gene expression and systolic blood pressure (SBP).

**Methods**

**Animals and Tissue**

All experiments were conducted in accordance with the Australian code of practice for the care and use of animals for scientific purposes as endorsed by the National Health and Medical Research Council of Australia. The Animal Care and Ethics Committee of the Royal North Shore Hospital approved all protocols. Eighteen animals were used in the study, which included Sprague-Dawley (SD, \(n=6\)), Wistar-Kyoto (WKY, \(n=6\)), and spontaneously hypertensive rats (SHR, \(n=6\)). SBP was measured at 18 weeks of age, 2 weeks before tissue isolation, using tail cuff plethysmography, an approach that we have validated using simultaneous femoral artery recording. Previous studies have demonstrated that SBP is significantly elevated in SHR from 16 weeks.\(^10\) Animals were euthanized with sodium pentobarbitone (90 mg/kg intraperitoneally), and tissue was removed without perfusing to avoid introducing inhibitors that might affect the reverse transcription-polymerase chain reaction (RT-PCR).

Tissue sections weighing less than 1 mg were taken from the renal medulla, myocardium, and adrenal medulla. Tissue punches of the hypothalamus centered on the ventromedial hypothalamus (VMH), rostral ventrolateral medulla (RVLM), and dorsal and intermediate thoracic spinal cord, including the intermediolateral cell columns, were taken from 1-mm-thick sections of the intermediolateral cell column, which were used as landmarks to indicate the position of the RVLM.  

**Tissue sections**

Adjacent sections of the thoracic spinal cord and lower brain stem and are also expressed in some peripheral tissues, but in lower amounts.\(^7\) Catabolism and reuptake of noradrenaline within the synaptic cleft is achieved either by the actions of the catabolic enzymes catechol-O-methyltransferase\(^8\) and monoamine oxidase\(^8\) or by the noradrenaline transporter (NAT), which has been localized to regions of the pons and medulla oblongata.\(^9\) The aims of this study were, first, to measure the levels in expression of the genes for PNMT, NAT, \(\alpha_{2A}\)-R, and \(\alpha_{2C}\)-R in hypertensive rats and compare them with normotensive rats at central and peripheral tissue sites that are involved in the sympathetic control of arterial blood pressure. Secondly, our aim was to determine if any relationship exists between levels of gene expression and systolic blood pressure (SBP).  

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by serially diluting (1:1, 1:10, and 1:100) cDNA from WKY and SHR in equal amounts, amplifying the GAPDH gene, and then comparing the Ct values (cycle threshold set where the exponential phase of the PCR reaction began) obtained for each strain. Equal Ct values indicated that the levels of GAPDH did not vary between strains. By plotting the Ct values for GAPDH (y) against the concentration of cDNA (x), a standard curve was generated from which the unknown amount of each gene expressed within the sample was determined.

Data Analysis

Data were normalized and all values are expressed as the amount of target as a percentage of GAPDH cDNA in the sample ± SEM for each strain of animal. An unpaired Student t test was used to determine if there were any significant differences between groups (α=0.05). To determine the relationship between systolic blood pressure and the relative amount of target gene, a correlation coefficient was determined in all strains for all tissues and targets. Regression curves were plotted for WKY (n=6) and SHR (n=6) using the systolic blood pressure of each animal against the level of gene expression for each animal.

Results

Tail cuff plethysmography showed that the SHR used in this study had significantly higher SBPs than the WKY and SD, whereas there was no difference in SBP between WKY and SD rats (SHR=150±12 mm Hg [n=6]; WKY=103±2 mm Hg [n=6]; SD=98±3 mm Hg [n=6]; P<0.001). Quantitative real-time PCR was successfully conducted on all cDNA samples with positive amplification of the GAPDH cDNA internal standard fragment (239 base pair [bp]), PNMT fragment (543 bp), NAT fragment (229 bp), α1A-R fragment (250 bp), and α2A-R fragment (337 bp) (Figure 1D). There were no nonspecific products observed in any of the samples and no genomic DNA amplification in RT negative controls (Figure 1D), which was further confirmed by a melt analysis of each product (data not shown).

Measurement of PNMT, NAT, α1A-R, and α2A-R cDNA within the 6 sites examined gave the results shown in Figures 2A through 2F. The first 3 sites examined were from central tissue known to be involved in the regulation of arterial blood pressure: the VMH, RVLM, and spinal cord. Figure 2A shows the data obtained from the VMH. No PNMT cDNA was found in any species within any of the VMH tissue samples. VMH tissue taken from SHR showed a significant increase in the amount of NAT and α1A-R cDNA compared with that taken from SD or WKY by a ratio of 7:1 and 2:1, respectively (WKY=0.03±0.003% [n=6], WKY=0.004±0.0001% [n=6]; P<0.0001; α1A-R: SHR=3.26±0.04% [n=6], WKY=1.42±0.07% [n=6], SD=1.46±0.05% [n=6], P<0.0001). However, the amount of α2A-R cDNA taken from SHR was significantly less than that found in SD or WKY by a ratio of 1:4 (α2A-R: SHR=1.35±0.05% [n=6], WKY=4.91±0.17% [n=6], SD=4.57±0.12% [n=6], P<0.0001). The second central site examined was the RVLM (Figure 2B). RVLM tissue punches taken from SHR demonstrated significant increases in PNMT, NAT, and α2A-R cDNA compared with that of SD or WKY by ratios of 3:1, 2:1, and 2:1, respectively (PNMT: SHR=0.82±0.02% [n=6], WKY=0.29±0.02% [n=6], SD=0.31±0.01% [n=6], P<0.0001; NAT: SHR=0.78±0.02% [n=6], WKY=0.37±0.01% [n=6], SD=0.31±0.02% [n=6], P<0.0001; α2A-R: SHR=4.10±0.11% [n=6], WKY=2.95±0.15% [n=6], SD=2.52±0.10% [n=6], P<0.001). As observed in VMH tissue samples, the amount of α2A-R cDNA in RVLM tissue samples taken from SHR was significantly less than that in SD or WKY by a ratio of 1:3 (α2A-R: SHR=1.38±0.04% [n=6], WKY=4.19±0.19% [n=6], SD=3.77±0.18% [n=6], P<0.0001). The final central site studied was the thoracic spinal cord (Figure 2C). There was no...
amplification of PNMT or NAT cDNA in any of the spinal cord tissue samples. Like the VMH and RVLM, the amount of α1A-R found in spinal cord tissue taken from SHR was significantly greater than that from SD or WKY by a ratio of 2:1 (α1A-R: SHR = 5.73 ± 0.11% [n = 6], WKY = 2.63 ± 0.05% [n = 6], SD = 2.46 ± 0.08% [n = 6]; P < 0.0001). Similarly, the amount of α2A-R cDNA was significantly lower in spinal cord tissue taken from SHR compared with that from SD or WKY by a ratio of 2:3 (α2A-R: SHR = 1.85 ± 0.04% [n = 6], WKY = 3.26 ± 0.07% [n = 6], SD = 2.98 ± 0.11% [n = 6]; P < 0.0001). A consistent pattern was observed in central tissue when the amount of α2A-R and α1A-R was investigated in normotensive and hypertensive animals. In normotensive animals the amount of α2A-R cDNA detected was significantly greater than the amount of α1A-R cDNA (P < 0.001, n = 6 in each group). In contrast, in the SHR the amount of α2A-R cDNA detected was significantly less than the amount of α1A-R cDNA (P < 0.001, n = 6 in each group).

Three peripheral sites were also investigated: the renal medulla, the heart, and the adrenal medulla. Results for tissue biopsies obtained from the renal medulla are shown in Figure 2D. There was no positive amplification of PNMT or NAT cDNA in any of the renal medullary tissue samples. Interestingly, tissue obtained from the renal medulla of SHR showed a significantly lower amount of α2A-R cDNA along with α1A-R cDNA compared with that from SD or WKY by ratios of 1:3 and 2:3, respectively (α1A-R: SHR = 1.94 ± 0.06% [n = 6], WKY = 4.86 ± 0.19% [n = 6], SD = 5.51 ± 0.15% [n = 6], P < 0.0001; α2A-R: SHR = 1.11 ± 0.04% [n = 6], WKY = 1.77 ± 0.06% [n = 6], SD = 1.96 ± 0.11% [n = 6], P < 0.0001). Only α1A-R and α2A-R cDNA could be amplified from the myocardium (Figure 2E). The amount of α1A-R cDNA detected in tissue taken from the myocardium of SHR was significantly greater than that from SD or WKY by a ratio of 2:1 (α1A-R: SHR = 7.13 ± 0.13% [n = 6], WKY = 5.00 ± 0.22% [n = 6], SD = 5.37 ± 0.15% [n = 6], P < 0.0001). The amount of α2A-R cDNA detected in myocardial tissue taken from SHR was significantly lower than that detected in SD or WKY by a ratio of 2.5 (α2A-R: SHR = 0.14 ± 0.01% [n = 6], WKY = 0.35 ± 0.02% [n = 6], SD = 0.34 ± 0.02% [n = 6], P < 0.001). Finally, we detected and measured the levels of PNMT, NAT, α1A-R, and α2A-R cDNA in adrenal medulla tissue (Figure 2F). In the adrenal medulla, the amount of PNMT, NAT, and α2A-R cDNA taken from SHR was significantly greater than in SD or WKY by a ratio of 1.5:1, 3:1, and 3:1, respectively (PNMT: SHR = 7.59 ± 0.09% [n = 6], WKY = 6.40 ± 0.11% [n = 6], SD = 6.57 ± 0.15% [n = 6], P < 0.01); NAT: SHR = 3.97 ± 0.10% [n = 6], WKY = 1.30 ± 0.04% [n = 6], SD = 1.29 ± 0.03% [n = 6], P < 0.0001; α1A-R: SHR = 7.47 ± 0.17% [n = 6], WKY = 2.76 ± 0.15% [n = 6], SD = 3.45 ± 0.10% [n = 6], P < 0.0001). The amount of α2A-R cDNA in adrenal medulla taken from SHR was significantly lower than that from SD or WKY by a ratio of 2.3 (α2A-R: SHR = 0.64 ± 0.02% [n = 6], WKY = 0.95 ± 0.03% [n = 6], SD = 0.94 ± 0.03% [n = 6], P < 0.001). Thus, similarly to the central pattern, peripheral tissue of SHR consistently showed α2A-R was less then α1A-R. In contrast, unlike the central tissue, the amount of α1A-R cDNA detected in peripheral tissue was significantly higher than the amount of α2A-R cDNA in normotensive and hypertensive strains (P < 0.001).

The relationship between systolic blood pressure and the level of gene expression in all strains and for all tissues was investigated. No significant correlation was observed in any of the normotensive tissue samples for any of the targets. In the SHR, however, there were significant correlations observed between SBP and the level of gene expression in a
number, but not all, of the tissues (Figures 3A through 3L). Within the VMH there was a positive and significant correlation between the amounts of NAT cDNA \((r^2=0.93, P<0.05, n=6, \text{Figure 3A})\) and \(\alpha_2A-R\) cDNA \((r^2=0.86, P<0.05, n=6, \text{Figure 3B})\), and SBP. The amount of \(\alpha_2A-R\) cDNA in VMH tissue was significantly and negatively correlated to SBP \((r^2=-0.82, P<0.05, n=6, \text{Figure 3C})\). RVLM tissue showed a positive and significant correlation between the amounts of PNMT \((r^2=0.91, P<0.05, n=6, \text{Figure 3D})\), NAT \((r^2=0.91, P<0.05, n=6, \text{Figure 3E})\), and \(\alpha_1A-R\) \((r^2=0.97, P<0.001, n=6, \text{Figure 3F})\) cDNA and SBP. The amount of \(\alpha_2A-R\) cDNA in RVLM tissue punches was significantly and negatively correlated to SBP \((r^2=-0.87, P<0.05, n=6, \text{Figure 3G})\). In the spinal cord, the amount of \(\alpha_1A-R\) cDNA was significantly and positively correlated to SBP \((r^2=0.97, P<0.001, n=6, \text{Figure 3H})\). Interestingly, in tissue taken from the renal medulla of SHR, the amount of \(\alpha_1A-R\) cDNA was significantly and negatively correlated to SBP \((r^2=-0.89, P<0.05, n=6, \text{Figure 3I})\). Myocardial tissue taken from SHR showed a positive and significant correlation between the amount of \(\alpha_1A-R\) cDNA and SBP \((r^2=0.98, P<0.001, n=6, \text{Figure 3J})\). Finally, there was a significant and positive correlation between the amounts of NAT cDNA \((r^2=0.97, P<0.001, n=6, \text{Figure 3K})\) and \(\alpha_2A-R\) cDNA \((r^2=0.90, P<0.05, n=6, \text{Figure 3L})\), and SBP in adrenal gland tissue taken from SHR.

**Discussion**

In the present study differences in the expression levels of the genes for PNMT, NAT, and \(\alpha_1A-R\) were always higher, and the levels of \(\alpha_2A-R\) were always lower in all tissue samples investigated in SHR compared with both normotensive strains (except for the \(\alpha_1A-R\) in the renal medulla). Despite the exception, the data suggests that the changes in gene expression between SHR and normotensive are global rather than site-specific. The genes were expressed at sites previously identified to contain cells that express the gene or its protein product. PNMT was expressed in RVLM punches and adrenal medullary tissue. Both adrenergic receptors were expressed in all tissue investigated. NAT was expressed in hypothalamus, RVLM, and adrenal medulla. In this study we have demonstrated for the first time that the levels of gene expression of PNMT, NAT, \(\alpha_1A-R\), and \(\alpha_2A-R\) within central tissue samples taken from SHR, but not so in SD or WKY, are significantly correlated to SBP, except for the \(\alpha_1A-R\) in the spinal cord. The range of SHR SBP was fortuitous in this randomly selected cohort. This contrasts with peripheral tissue where only 4 correlations out of a possible 8 were significant. The lack of any significant correlation between the expression of targeted genes and SBP in WKY or SD could be due to the small range in SBPs observed for each strain (eg, 101 to 105 mm Hg for WKY). Therefore, it is still conceivable that, although no correlation was observed for the group data of SD or WKY, a small relationship might be uncovered if a larger population were to be investigated.

The VMH, RVLM, and intermediolateral cell column of the spinal cord all play important roles in cardiovascular control and represent second- and third-order neurons and presympathetic and sympathetic neurons, respectively. The results suggest that, within central tissue sites related to cardiovascular control, there appears to be a strong relationship between the levels of each catecholaminergic-related gene transcribed and SBP. In this study we have found a significant increase in PNMT and NAT mRNA levels in the RVLM of SHR compared with WKY. Previously we demonstrated a similar finding for TH. Furthermore, the level of 3 genes whose products are involved in the synthesis or uptake of catecholamines in the RVLM were significantly and positively correlated to SBP. NAT neurons found in the RVLM comprise a small minority of C1 cells. Although Lorang et al, using hybridization histochemistry, suggest that NAT is not expressed in C1 neurons, Comer et al, using carefully devised single-cell PCR studies, found that NAT was expressed in 10% of identified bulbospinal C1 neurons. In the present study, it is still possible that some of the NAT gene expression within the RVLM originated from stray A1 neurons. Angiotensin II induces higher levels of NAT mRNA in SHR than in WKY and causes an increase in MAP when injected into the RVLM. Consistent with this observation, we find an increase in NAT in SHR compared with WKY. Increases in TH, PNMT, and NAT mRNA suggest a heightened activation of the adrenergic system in SHR RVLM, with increased production of noradrenaline and adrenaline, along with an increased reuptake of catecholamines from the synaptic cleft. That this is a global upregulation of catecholamine synthesis and uptake is supported by similar findings from the VMH (NAT) and the adrenal medulla (NAT and PNMT).

\(\alpha_1A-R\) and \(\alpha_2A-R\) are 2 of a family of receptors that are responsible for mediating the effects of noradrenaline and adrenaline. They are both strongly implicated in the control of arterial pressure although other subtypes may also play a role as evidenced from experiments in transgenic animals. Both \(\alpha_2A-R\) agonists cause a centrally mediated hypotension and bradycardia via \(\alpha_2A-R\) and peripherally derived hypertension via \(\alpha_2C-R\). \(\alpha_2C-R\) knockout mice have increased heart rates and blood pressure as well as elevated plasma catecholamines. \(\alpha_2A-Rs\) are also found at select peripheral locations and are commonly presynaptic. \(\alpha_1A-Rs\) found in central tissue are generally postsynaptic and thought to be stimulatory in nature. They also play a dominant role in the periphery where they regulate contraction of smooth muscle associated with particular vessels, particularly the renal arteries. In support of this, \(\alpha_1A-R\) knockout mice show a decrease in mean arterial pressure and a decreased response to the \(\alpha_1A-R\) agonist, phenylephrine. Here we find in SHR that the amount of \(\alpha_1A-R\) is significantly greater, whereas the amount of \(\alpha_2A-R\) gene expression is significantly lower compared with normotensive rats in all tissue except the renal medulla. These results strongly support the observations of Tavares et al, who demonstrated, using in situ hybridization (ISH), 20% less \(\alpha_2A-R\) within the pons-medulla of SHR compared with WKY and Bottiglieri et al, who used ISH to demonstrate higher amounts of \(\alpha_1A-R\) gene expression in the hypothalamus and neuronal cultures of SHR, respectively. However, the key advantages to our method compared with those used by Tavares et al and others is that we are able to accurately measure smaller amounts of RNA and are therefore able to...
measure gene expression in smaller site-specific regions. The pattern of gene expression seen is evident for all related genes in central tissues associated with cardiovascular control, but particularly in the RVLm. In central tissue of normotensive animals, the α2A-R is dominant. Data from the present study is consistent with the idea that the level of sympathetic outflow may be due to the balance of α1A-R and α2A-R, because α1A-R are found at higher levels in SHR, and α2A-R are found at lower levels in this strain at all sites examined. This idea is supported by the observations that genetically manipulated mice that lack the α2A-R become hypertensive at a faster rate under a salt diet than that of their wild-type counterparts.

The only tissue that stood out in our six sample sites was the renal medulla. Here the amount of α2A-R cDNA amplified in renal medulla tissue samples taken from SHR was significantly lower compared with SD or WKY. The lower levels of α2A-R gene expression observed in SHR renal medulla tissue could be due to the heterogeneity of the kidney itself. The renal medulla contains blood vessels and parts of the renal tubular system that possess specialized cells for the regulation of an osmotic gradient that is important to the kidney’s ability to produce urine of various concentrations. We speculate that a decrease in α1A-R would lead to a decrease in glomerular blood pressure and therefore lead to an increased conservation of fluid and salt, causing blood pressure to rise. Alternatively, a complex change in the expression of α2A-R on different parts of the renal vasculature could account for the apparently paradoxical effects seen in this tissue.

In this study, selective regional differences were identified in the levels of gene expression between hypertensive and normotensive animals. Furthermore, in SHR there were significant correlations with SBP in some, but not all, sites examined. Whether or not these relationships are causes of, effects of, or simply incidental to, the differences in arterial examined. Whether or not these relationships are causes of, effects of, or simply incidental to, the differences in arterial

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