Proton Magnetic Resonance Spectroscopy Detection of Neurotransmitters in Dorsomedial Medulla Correlate With Spontaneous Baroreceptor Reflex Function

Maria A. Garcia-Espinosa, Hossam A. Shaltout, John Olson, Brian M. Westwood, Mike E. Robbins, Kerry Link, Debra I. Diz

Abstract—Control of heart rate variability via modulation of sympathovagal balance is a key function of nucleus tractus solitarii and the dorsal motor nucleus of the vagus localized in the dorsomedial medulla oblongata. Normal blood pressure regulation involves precise balance of glutamate (Glu)-glutamine-\(\gamma\)-aminobutyric acid transmitter systems, and angiotensin II modulates these transmitters to produce tonic suppression of reflex function. It is not known, however, whether other brain transmitters/metabolites are indicators of baroreflex function. This study establishes the concept that comprehensive baseline transmitter/metabolite profiles obtained using in vivo \(^1\)H magnetic resonance spectroscopy in rats with well-characterized differences in resting blood pressure and baroreflex function can be used as indices of autonomic balance or baroreflex sensitivity. Transgenic rats with over-expression of renin \([m\text{Ren2}]^{27}\) or under-expression of glial-angiotensinogen (ASrAogen) were compared with Sprague-Dawley rats. Glu concentration in the dorsal medulla is significantly higher in ASrAogen rats compared with either Sprague-Dawley or \([m\text{Ren2}]^{27}\) rats. Glu levels and the ratio of Glu:glutamine correlated positively with indices of higher vagal tone consistent with the importance of these neurotransmitters in baroreflex function. Interestingly, the levels of choline-containing metabolites showed a significant positive correlation with spontaneous baroreflex sensitivity and a negative correlation with sympathetic tone. Thus, we demonstrate the concept that noninvasive assessment of neurochemical biomarkers may be used as an index of baroreflex sensitivity. (Hypertension. 2010;55[part 2]:487-493.)

Key Words: hypertension ■ baroreflex sensitivity ■ \(^1\)H MRS ■ brain ■ neurotransmitters

Proton magnetic resonance spectroscopy (\(^1\)H-MRS) has emerged as a powerful tool to investigate brain neurochemistry. An interesting component of this noninvasive technique, other than high-resolution anatomic imaging, is the quantitative analysis of the neurochemistry of discrete brain areas.\(^1\) Many studies have reported the use of \(^1\)H MRS to detect amino acids, lipids, and other metabolites in the brain.\(^2\)-\(^6\) Few studies have addressed the balance of these and other neurotransmitters in animals with long-term alterations in the renin-angiotensin (Ang) system, and none have used localized spectral analysis by nuclear magnetic resonance in rats or mice to link transmitters with cardiovascular function in a predictive manner. Moreover, invasive techniques with an indwelling brain, arterial catheters, or dialysis probes have been required.

The amino acid neurotransmitters glutamate (Glu) and \(\gamma\)-aminobutyric acid (GABA) are present in areas involved in cardiovascular regulation, most notably the medullary sites involved in baroreceptor and chemoreceptor actions. Glu is at least 1 of the neurotransmitters released from both baroreceptor and chemoreceptor afferent fibers projecting to the nucleus of the solitary tract (nTS) from the vagal and glossopharyngeal nerves.\(^7\) Glutamatergic nTS neurons excite both the rostral ventrolateral medulla and caudal ventrolateral medulla, whereas GABA-ergic nTS and caudal ventrolateral medulla neurons inhibit the sympathetic activity of the rostral ventrolateral medulla neurons.\(^8\) GABA release in the nTS is thought to impair baroreflex function and may mediate the effects of angiotensin (Ang) II to suppress baroreflex sensitivity (BRS).\(^9\),\(^10\)

In previous studies we have shown that both aging and hypertension in rats are associated with impairment of BRS for control of heart rate (HR) and the responses to cardiac vagal chemosensitive fiber activation. Impairments in BRS may contribute to decreases in HR variability (HRV) and increases in blood pressure variability (BPV), key risk factors in the development of hypertension and stroke. In this study we took advantage of 3 strains of rats with different and

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well-characterized phenotypes for cardiovascular and autonomic function. ASrAogen transgenic rats, with targeted disruption of glial angiotensinogen and low brain tissue Ang I and Ang II, have low resting mean arterial pressure (MAP) and better BRS and responses to chemosensitive fiber activation, as compared with control Sprague-Dawley rats. In contrast, (mRen2)27 transgenic rats with overexpression of a mouse renin transgene and high levels of brain tissue Ang II develop hypertension and have an impaired BRS and responses to chemosensitive fiber activation. At present, performing a functional evaluation of changes in brain neurochemistry simultaneous with hemodynamic measures is not an easy task. Our goal was to establish the concept that relationships exist between BRS and indices of autonomic function and dorsal medullary neurotransmitter/metabolites as detected by $^1$H MRS and that these metabolite profiles could be used as noninvasive markers of different cardiovascular phenotypes.

### Methods

#### Animals and Surgical Procedures

Male Sprague-Dawley, (mRen2)27, and ASrAogen rats (n = 3 per strain, 20 to 30 weeks old) with different and well-characterized phenotypes for blood pressure and BRS were included in this study to provide a range of values for autonomic function variables. The animals were obtained from the Wake Forest University Hypertension and Vascular Research Center Transgenic Animal Facility and housed in an American Association for Accreditation of Laboratory Animal Care–approved facility with controlled temperature, light-dark cycles (12 hour), and food and water ad libitum. All of the procedures were approved by the Wake Forest University School of Medicine Institutional Animal Care and Use Committee. Anesthesia was induced with isoflurane and polyethylene catheters (phycoerythrin 50 tubing; Clay Adams) placed into the femoral artery and vein, exteriorized at the subscapular area, and secured. The animals were allowed to recover for ≥ 48 hours before the $^1$H MRS experiments. $^1$H MRS experiments were done under 1.5% isoflurane anesthesia.

#### Blood Pressure Recording and Spontaneous Baroreflex Study

Pulsatile arterial pressure was acquired via strain gauge transducer connected to an arterial catheter and data acquisition system (Acknowledge software version 3.7.2, BIOPAC System Inc) in anesthetized rats. HR was determined from the arterial pressure wave. Spontaneous BRS was calculated by the frequency-domain analysis method using software designed for rats (Nevrokard SA-BRS, Medistar), as reported in our previous work. In brief, power spectral densities of systolic arterial pressure (SAP) and RR interval (RRI) were computed by 512-point fast Fourier transform and integrated over the specified frequency range for rats (low frequency [LF]: 0.25 to 0.75 Hz) and (high frequency [HF]: 0.75 to 3.0 Hz). A Hanning window was applied, and the spectra of SAP and RRI series, as well as their squared-coherence modulus, were computed if the coherence was > 0.5, in accordance with reported criteria. The square roots of the ratio of RRI and SAP powers were computed to calculate LF and HF $\alpha$ indices, which reflect the BRS. The power of RRI spectra in the LF and HF range (LF$_{RRI}$ and HF$_{RRI}$) was calculated in normalized units, and the ratio of LF$_{RRI}$/HF$_{RRI}$ was used as a measure of sympathovagal balance. The power of SAP spectra was calculated as LF$_{SAP}$ as a measure of BVP. HRV was also determined by computing the SD of a beat-to-beat interval and the root mean square of successive beat-to-beat differences in beat-to-beat interval duration. The SD of the MAP (SDMAP) was used as a measure for BVP. Three time-domain parameters were used to measure hemodynamic variability, as in previous studies. BRS was calculated by sequence methods on the basis of quantification of sequences of ≥ 3 beats (n) in which SAP consecutively increases (up sequence) or decreases (down sequence), which are accompanied by changes in the same direction of the RRI of the subsequent beats (n + 1).  

#### In Vivo $^1$H MRS

A 7-T horizontal bore small animal MRI scanner was equipped with a high-performance gradient insert capable of generating a maximum gradient strength of 400 mT/m (Bruker Biospin). A litzcage radiofrequency coil with an ID of 38 mm tuned to 300.2 MHz was used to send and receive magnetic resonance signals (Doty Scientific Instruments). Respiration, temperature, and cardiac period were followed using probes, interface hardware, and small animal monitoring software (SA Instruments). Temperature of the animal inside the magnet was maintained at 37.5°C with thermostatically controlled warm air blown into the bore of the scanner (SA Instruments). The animals were anesthetized using isoflurane (3% ) and oxygen (4 L/min) and were maintained with 1.5% isoflurane and 1 L/min of oxygen. The imaging protocol includes a spin echo localization sequence with a repetition time of 2500 ms, an echo time of 30 ms, a 128×128 matrix, and a field of view of 4.0 cm. The number of excitations was 1, followed by a rapid acquisition with relaxation enhancement spin echo with a echo train length of 8 T2-weighted localizers in the axial and sagittal planes (repetition time: 2500 ms; echo time: 55 ms; 256×256 matrix; field of view: 3.5 cm; number of excitations: 4). The spectra are acquired using a position resolved spectroscopy sequence repetition time of 2500 ms, an echo time of 20 ms, and a cubic voxel of 27 mm$^3$, with the number of excitations at 640. The dimensions of the voxel would include nTS, dorsal motor nucleus of the vagus, and hypoglossal nucleus as a major nuclei in the sampling area. The water suppression module consisted of variable pulse power and optimized relaxation delays. The spectra were processed and quantified using the LC model package on a basis set provided by Provencher and in-house written MATLAB code. Metabolites were chosen for quantification on the basis of their respective percentage SDs, which are commonly used as the most dependable parameters for quantification reliability. Metabolites with a percentage SD of ≥ 20 have been used as the criterion for acceptable reliability, especially for signals difficult to resolve, such as GABA, Glu, Gln, phosphocreatine, and creatine, as published by us previously.

Most uses of $^1$H MRS comparing changes in animals after an intervention rely on ratios of metabolites to some stable internal compound (usually creatine or phosphocreatine+c creatine). However, in our studies of 3 strains of rats, we were concerned that baseline differences may exist. Therefore, we prepared standards of known concentrations (phantoms) of the metabolites of interest, and spectra were acquired using the same imaging protocol as the animals for accurate quantification of the concentration of the metabolites and transmitters in millimoles. The phantom consists of a 50-mL tube designed to approximate the radiofrequency coil loading when a rat is being scanned. It contains the main brain metabolites that are observable in an $^1$H MRS in vivo (Glu, N-acetyl aspartate [NAA], Myo-inositol, creatine, and choline). As for the differences in T1 and T2 between in vivo and in vitro conditions, on the one hand, a paramagnetic agent (Gadolinium-Diethylenetriamine penta-acid) was added to the solution (0.5 mmol/L), which reduces both T1 and T2, thus approximating them to those in vivo. On the other hand, the echo time used for the acquisition of the spectra was short (20 ms), which assures that the signal decay attributed to T2 effects is minimized.

#### Data Analysis and Statistics

One-way ANOVA was used for measures among strains followed by appropriate post hoc analyses. For assessment of complex relationships among the variables studied, the entire data set was analyzed by correlate summation analysis (CSA). CSA is a data mining method.
designed to find the variables that are most covariant with all of the other variables being studied, relative to clustering. This provides an alternative method to yield important variables and data clustering comparable to PCA without the need for specialized computer packages.28 There is a freely available correlate summation Microsoft Excel template that performs a CSA for \( \leq 100 \) variables for 4 groups of 15 subjects (http://en.wikipedia.org/wiki/Correlate_summation_analysis).

Specifically with these data, aggregate correlate summation was applied to the regression analyses. Treating the 3 animal models as a continuum of perturbation of the renin-angiotensin-system, the degree of variable relationships was compared relative to normalized spread in the data (as a clustering proxy). Aggregate correlate summation rank was used to short the variables for a layered correlation matrix/dedimensionalized groupwise descriptive statistics plot to aid a parsing of the data (dedimensionalized data reduced by the mean of all of the subjects independent of group, for each variable). This new visualization technique highlights the use and concept behind aggregate correlate summation by aggregating correlations to the upper left quadrant and means clustering diminishing to unity (left to right).

Results
Metabolite Levels in Dorsal Medullary Tissue of Sprague-Dawley, (mRen2)27, and ASrAogen Rats
In vivo \(^1\)H spectra were collected from Sprague-Dawley, (mRen2)27, and ASrAogen rats. An example of the spectrum of a Sprague-Dawley rat is shown in Figure 1. GABA, Glu, NAA, N-acetyl aspartyl Glu (NAAG), creatine/phosphocreatine, myo-inositol, and taurine signals were resolved as reported previously using the LC model package.3,5,14,25 Phantoms were run to allow quantification of the metabolites, and Table 1 shows concentrations of neurotransmitters/metabolites in the animals measured at baseline. Many of these variables showed good reproducibility among the 3 animals within the same strain. Glu concentration was significantly higher in the dorsal medulla of the ASrAogen rats compared with Sprague-Dawley rats.

Table 1. Neurotransmitter/Metabolite Concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Concentration, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nt/Mt</td>
<td>SD</td>
</tr>
<tr>
<td>NAA</td>
<td>9.2 ± 0.3</td>
</tr>
<tr>
<td>NAA+NAAG</td>
<td>12.9 ± 0.2</td>
</tr>
<tr>
<td>Glu</td>
<td>8.4 ± 2.1</td>
</tr>
<tr>
<td>Glu+Gln</td>
<td>12.5 ± 1.1</td>
</tr>
<tr>
<td>GABA</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Cr</td>
<td>6.4 ± 5.5</td>
</tr>
<tr>
<td>Cr+PCr</td>
<td>11.3 ± 0.5</td>
</tr>
<tr>
<td>mIno</td>
<td>10.4 ± 0.7</td>
</tr>
<tr>
<td>Tau</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>GPC+PCh</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>

MAP and HR in Sprague-Dawley, (mRen2)27, and ASrAogen Rats
Compared with Sprague-Dawley rats, MAP under isofluorane was similar in (mRen2)27 and higher in ASrAogen rats (mean ± SEM: 91 ± 2, 90 ± 1, and 105 ± 3 mm Hg for Sprague-Dawley, [mRen2]27, and ASrAogen rats, respectively). HR was 27% lower in the (mRen2)27 rats and 13% higher in ASrAogen rats compared with Sprague-Dawley rats (mean ± SEM: 256 ± 22, 182 ± 4 and 288 ± 7 bpm for Sprague-Dawley, [mRen2]27, and ASrAogen rats, respectively). These measurements are consistent with observations reported previously1,28 under chloralose-urethane anesthesia.

BRS, HRV, and BPV
Autonomic function and spontaneous BRS were determined using both spectral analysis and sequence methods (Figure 2). The mean LF-\( \alpha \) index was 42% higher in (mRen2)27 rats compared with Sprague-Dawley rats, which is consistent with greater activation of the sympathetic arm in these animals. No differences in LF-\( \alpha \) were observed between the Sprague-Dawley and the ASrAogen groups. ASrAogen rats showed a higher HF-\( \alpha \) index when compared with both Sprague-Dawley (87%) and (mRen2)27 (83%) animals, which is consistent with higher parasympathetic tone in ASrAogen animals. Sympatho-vagal balance, measured by LF_HF ratio (Figure 2), was higher in the hypertensive (mRen2)27 group, which is in keeping with exacerbated cardiac sympathetic activity. In contrast, ASrAogen rats showed a lower LF_HF ratio suggesting a shift of the sympatho-vagal balance toward an improved vagal component. BRS, measured by the sequence method (sequence up, down, and total), is higher in ASrAogen rats. In contrast, (mRen2)27 rats did not show differences for any of the BRS indices compared with Sprague-Dawley animals. HRV and BPV, as measured
by the time domain method, were not different between the strains (data not shown). These results are consistent with previous reports using these and other methods indicating that BRS for HR control (vagal tone) is higher in ASrAogen rats and lower in (mRen2)27 rats relative to Sprague-Dawley rats, with high cardiac sympathetic tone in the (mRen2)27 rats.14,15

Regression Analysis and CSA of Metabolites and Hemodynamic Parameter in Sprague-Dawley, (mRen2)27, and ASrAogen Rats

An important goal of this study was to determine whether the neurotransmitter/metabolite profiles determined by 1H MRS correlate with measures of autonomic function. Therefore, spontaneous BRS, HRV, BPV, and sympathovagal balance indices, together with the quantitative analysis of neurotransmitter/metabolite levels, were analyzed by linear regression (Table 2). For these analyses, we pooled the data from all 3 strains of the rats for a total of 9 animals. In addition, we used CSA to understand the relative degree of correlation among variables (Figure 3).

Glu levels and the ratio of Glu:Gln correlated positively with sequence all index (Seq All), suggesting the importance of these neurotransmitters in the functioning of the BRS (Table 2 and Figure 4). Of note, ASrAogen rats, which show better BRS, had the highest Glu levels and Glu/Gln ratio compared with the Sprague-Dawley and (mRen2)27 rats (Figure 4). Interestingly, the levels of choline-containing metabolites (tCho or GPC+PCh [glycerophosphocholine plus phosphocholine]) also showed a positive correlation with Seq All (Figure 4). ASrAogen rats showed higher levels of choline-containing compounds compared with (mRen2)27 rats (Table 1 and Figure 4). Finally, a negative correlation was observed between the cardiac sympathetic index LF/HF and the choline metabolites (Table 2).

Discussion

Our main finding is that neurotransmitter levels detected by in vivo 1H MRS correlate with indices of autonomic function in a sample of animals with a range of phenotypes for cardiovascular function. The medullary tissue concentrations of Glu, Gln/Gln, and choline-related compounds correlate positively with indices of vagal function, whereas choline-containing metabolites values show an inverse relationship with indices of sympathetic function.

As expected, the Glu-glutamine (Gln) transmitter system was a strong indicator of the vagal component of autonomic function. Glu levels and the ratio of Glu/Gln correlated positively with Seq All, confirming the importance of these neurotransmitters in the functioning of the BRS.9,10,29 Of note, ASrAogen rats, which show better BRS and highest vagal function,11,12,14,30 had the highest Glu levels and Glu/Gln ratio compared with the Sprague-Dawley and (mRen2)27

Table 2. Regression Analysis

<table>
<thead>
<tr>
<th>N/Mt</th>
<th>BRS or SB</th>
<th>P</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>Seq down</td>
<td>&lt;0.05</td>
<td>0.717</td>
</tr>
<tr>
<td>Glu</td>
<td>Seq all</td>
<td>&lt;0.05</td>
<td>0.706</td>
</tr>
<tr>
<td>Glu/Gln</td>
<td>Seq down</td>
<td>&lt;0.05</td>
<td>0.787</td>
</tr>
<tr>
<td>Glu/Gln</td>
<td>Seq down</td>
<td>&lt;0.05</td>
<td>0.796</td>
</tr>
<tr>
<td>Glu/Gln</td>
<td>Seq up</td>
<td>&lt;0.001</td>
<td>0.823</td>
</tr>
<tr>
<td>GPC+PCh</td>
<td>Seq down</td>
<td>&lt;0.05</td>
<td>0.751</td>
</tr>
<tr>
<td>GPC+PCh</td>
<td>Seq all</td>
<td>&lt;0.05</td>
<td>0.804</td>
</tr>
<tr>
<td>GPC+PCh</td>
<td>LF/HF</td>
<td>&lt;0.05</td>
<td>-0.68</td>
</tr>
</tbody>
</table>

Regression analysis of neurotransmitter/metabolite concentration (N/Mt) and metabolites ratios detected by 1H MRS and indices of BRS or sympathovagal balance (SB) determined by spectral analysis and sequence methods. Summary table shows the P values and correlation coefficients, R, of variables with positive or negative relationships. Seq indicates sequence.
GABA tended to show an inverse relationship. GABA release in the nTS is thought to impair baroreflex function and may mediate the effects of Ang II to suppress BRS, quite consistent with the trend for lower levels of this transmitter in the ASrAogen rats. Ang II is known to influence Glu release, and Ang-(1-7) modulates the release of Glu and taurine at the caudal ventrolateral medulla. Ang II releases substance P from brain medulla, and this neuropeptide also has interactions with taurine and other excitatory neurotransmitters. However, we observed no relationship between these transmitters and any of the indices of autonomic function in the brain area.

Interestingly, the levels of choline-containing metabolites (tCho [choline-containing metabolites] or GPC/PCh [glycerophosphocholine plus phosphocholine]) were found to be inversely correlated with the indices of baroreflex function. Figure 3 shows the linear regression between these transmitters and the indices of autonomic function. Figure 4 provides a comprehensive summary of the correlations observed between the neurotransmitter/metabolite concentrations and the indices of baroreflex function. The significant linear correlations are indicated by solid shading, while the negative relationships are shown in hatched shading. The variables measured include PCr/Cr (phosphocreatine/creatine ratio), LF/FRF (low frequency ratio of beat-to-beat interval), Tau (taurine), Cr (creatine), bsln (baseline), Seq up bsln (sequence up index baseline), Seq down bsln (sequence down baseline), Seq all bsln (sequence all baseline), GABA/GLU bsln (GABA/glutamate ratio baseline), SDRR (SD of the beat-to-beat interval), rMSSD (root mean square of successive beat-to-beat interval), and Ins (Inositol).
phosphocholine plus phosphocholine]) also showed a positive correlation with Seq All (Figure 4). AStrAogen rats showed higher levels of choline-containing compounds compared with (mRen2)27 rats. The choline signal intensity, detected by in vivo \(^1\)H MRS, has been shown to be positively correlated with levels of acetylcholine, as measured by high-performance liquid chromatography and microdialysis in the hippocampus, striatum, frontal cortex, and somatosensory barrel field cortex of rats.\(^{34}\) These data together suggest that acetylcholine neurotransmission could be associated with BRS function in the dorsomedial medulla. In addition, GPC+PCh (glycerophosphocholine plus phosphocholine) correlated negatively with LF\(_{\text{RRI}}\); HF\(_{\text{RRI}}\), which is an index of sympathovagal balance. Therefore, increased acetylcholine neurotransmission may be associated with not only improved BRS but also with increased parasympathetic activity.

Although we detected significantly higher Glu concentrations in the dorsal medulla of the AStrAogen rats, this study was not powered to detect differences among the 3 strains for the wide range of substances measured. A larger sample size will be required to determine whether there are any significant differences in baseline neurotransmitter/metabolite concentrations among strains. However, the intent of the study was to use the power of the 9 test animals to illustrate the correlations between transmitters and the indices of autonomic function. Strong (r>0.7) correlation coefficients were detected with the Glu-Gln system, suggesting that these may serve as effective predictors of the vagal phenotype. The CSA further demonstrates that metabolites associated with energy metabolism, such as phosphocreatine and NAA, are associated with vagal function (HF-). Strong (r>0.7) correlation coefficients were 

Potential correlations.

Perspectives

These preliminary data illustrate that quantitative in vivo \(^1\)H MRS provides important information about the neurotransmitters and metabolites existing in the dorsomedial medulla of rats during simultaneous assessment of autonomic function in animals with different cardiovascular phenotypes. In the future, perhaps stronger magnets and improved software will allow smaller voxel size assessments more closely associated with individual brain nuclei and over shorter time frames without compromising the resolution of the spectra. Whether the current measures provide mechanistic information about specific transmitter function in a specific nucleus remain to be determined. However, the data show that strong correlations exist that track with BRS in spite of the large area of medulla studied. Therefore, this technique will facilitate repeated noninvasive profiling of transmitter levels longitudinally that may be predictive of baroreflex/autonomic function, obviating the need for extensive instrumentation of rats now required to obtain the information on autonomic function.

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Disclosures

None.

References


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