Norepinephrine reuptake, baroreflex dynamics, and arterial pressure variability in rats

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Bertram, Delphine, Christian Barrès, Yong Cheng, and Claude Julien. Norepinephrine reuptake, baroreflex dynamics, and arterial pressure variability in rats. Am J Physiol Regulatory Integrative Comp Physiol 279: R1257–R1267, 2000.—This study examined the effect of norepinephrine reuptake blockade with desipramine (DMI) on the spontaneous variability of the simultaneously recorded arterial pressure (AP) and renal sympathetic nerve activity (SNA) in conscious rats. Acute DMI administration (2 mg/kg iv) depressed AP Mayer waves (0.2 Hz) and increased low-frequency (<0.2 Hz) components of AP variability. DMI decreased renal SNA variability, especially due to the abolition of oscillations related to Mayer waves. To examine whether DMI-induced changes in AP and renal SNA variabilities could be explained by alterations in the dynamic characteristics of the baroreceptor reflex loop, the frequency responses of mean AP to aortic depressor nerve stimulation were studied in urethan-anesthetized rats. DMI accentuated the low-pass filter properties of the transfer function without significantly altering the fixed time delay. The frequency responses of iliac vascular conductance to stimulation of the lumbar sympathetic chain were studied in an additional group of anesthetized rats. DMI did not markedly alter the low-pass filter properties of the transfer function and slightly increased the fixed time delay. These results suggest that the DMI-induced decrease in the dynamic gain of the baroreceptor reflex is responsible for the decreased spontaneous renal SNA variability and the accompanying increased AP variability. The “slowing down” of baroreflex responses cannot be attributed to an effect of DMI at the vascular neuroeffector junction.

aortic depressor nerve; desipramine; Mayer waves; spectral analysis; renal sympathetic nerve activity

THE ARTERIAL BARORECEPTOR reflex is the main mechanism limiting short-term arterial pressure (AP) variability (10), mainly through the sympathetic control of regional vascular resistances (33, 34). In addition to this major stabilizing role, the reflex is also involved in the production of rhythmic AP fluctuations, commonly referred to as Mayer waves, at frequencies close to 0.4 Hz in rats (8, 18). Recently, we provided experimental evidence that the baroreflex loop of the rat has the potential for generating a self-sustained oscillation at this frequency, especially because of a fixed time delay between baroreceptor afferent activity and AP (3). Consequently, any alteration in this fixed time delay is expected to induce a change in the frequency of AP Mayer waves. As an experimental testing of this hypothesis, we examined the acute effects of desipramine (DMI) administration on the harmonic components of AP variability in rats (4). Specifically, we hypothesized that DMI, by reducing the removal rate of norepinephrine (NE) at vascular neuroeffector junctions, would increase the time delay in the baroreflex loop and consequently would decrease the central frequency of Mayer waves. It was indeed observed that DMI abolished AP Mayer waves and markedly enhanced low-frequency variability around 0.1 Hz (4). According to our hypothesis, this could result from a shift of sympathetically mediated oscillations from 0.4 to 0.1 Hz. However, it could not be excluded in this study that DMI enhanced preexisting slow oscillations of AP around 0.1–0.15 Hz, such as those described by Janssen and colleagues (20), which have been ascribed to myogenic responses in the mesenteric and renal circulations (20, 23).

A first series of experiments was designed to examine whether DMI caused changes in the spontaneous variability of sympathetic nerve activity (SNA) that paralleled those in AP variability, i.e., a shift of spectral power from 0.4 to 0.1 Hz. In these experiments, the activity of the renal sympathetic nerve was taken as a reflection of the overall SNA in conscious rats (1, 6). A second series of experiments was performed in anesthetized rats to investigate the effect of DMI on the dynamic characteristics of the baroreceptor reflex and more specifically to determine whether DMI actually shifts the feedback oscillation frequency of the baroreflex loop from 0.4 to 0.1 Hz. In this study, we determined the frequency responses of AP to aortic depressor nerve stimulation (3) before and after DMI administration. Finally, as a direct test of our working hypothesis, we examined the effect of DMI on the...
frequency responses of resistance vessels to sympathetic modulation. In this experiment, we measured iliac blood flow during electrical stimulation of the lumbar sympathetic chain.

METHODS

A total of 22 male Sprague-Dawley rats (Iffa-Credo, L'Arbresle, France) weighing 300–350 g were used. On completion of the experiments, rats were killed with an intravenous overdose of pentobarbital sodium.

All experiments conformed to the guidelines of the French Ministry of Agriculture for animal experimentation.

Effect of DMI on Short-Term Variability of Mean AP and Renal SNA in Conscious Rats

Chronic instrumentation. Under halothane anesthesia (1.5–2% in oxygen), femoral arterial and venous catheters were inserted into the lower abdominal aorta and the inferior vena cava for AP measurement and drug administration, respectively. Catheters were led subcutaneously to exit at the back of the neck. Each rat was then placed in a large individual recording cage. After 1 full day of recovery, rats were reanesthetized with pentobarbital sodium (60 mg/kg iv). Through a flank incision, a branch of the left renal sympathetic nerve was dissected free, placed on a bipolar platinum-iridium electrode, and insulated with a silicone gel (604A and B; Wacker Chemie, München, Germany). The electrode cable was secured to back muscles and exteriorized at the nape of the neck. The plug was protected in a small cap sewn to the skin. Rats were allowed to recover overnight from anesthesia.

Recording protocol. AP was measured with a pressure transducer (TFN-R; Ohmeda, Bilthoven, The Netherlands) coupled to an amplifier (model 13–4615–52; Gould, Cleveland, OH). The renal SNA signal was amplified (50,000×; model P-511 J, Grass, Quincy, MA), band-pass filtered (100–1,000 Hz), rectified, and further low-pass filtered at 5 Hz. AP and renal SNA were recorded simultaneously to a chart recorder (model 8802; Gould) and to a personal computer via an analog-to-digital converter board (model AT-MIO-16; National Instruments, Austin, TX). With LabVIEW 4.0 software (National Instruments), both signals were sampled at 500 Hz. After stabilization of cardiovascular variables, AP and renal SNA were recorded for 1 h under control conditions. Then the patency of the venous catheter was verified with an injection of phenylephrine (3 μg/kg iv), and DMI hydrochloride (2 mg/kg iv) was administered. Cardiovascular variables were again recorded for 1 h. The 2 mg/kg dose of DMI has been shown previously to almost completely abolish pressor responses to tyramine (250 μg/kg iv) for at least 1 h in conscious rats (4). Finally, the background noise of renal SNA was determined as the minimum activity recorded after administration of the ganglionic blocker trimethaphan (10 mg/kg iv). From each 1-h recording period, 30 min of rest were selected for further analysis.

Data analysis. The computer (Sparc1; Sun Microsystems, Mountain View, CA) generated beat-to-beat time series of mean AP that were then resampled at 10 Hz after linear interpolation. Renal SNA data were averaged over consecutive 100-ms periods, the background noise was subtracted, and all values were then normalized by the mean value measured under control conditions. For both mean AP and renal SNA, the 10-Hz time series were segmented into 2,048-point (204.8 s) periods overlapping by half. Fast Fourier transform analysis was performed as previously described (4, 23). Total (0–5 Hz, referred to as overall variability), low (LF, 0.005–0.269 Hz), mid (MF, 0.273–0.742 Hz), and high (HF, 0.747–5 Hz)–frequency powers were calculated by integration. The squared coherence function, which quantifies the amount of linear coupling between variables, was also calculated (8).

Effect of DMI on the Frequency Responses of Mean AP to Aortic Depressor Nerve Stimulation in Anesthetized Rats

Surgical procedures. Rats were anesthetized with urethane (1.2 g/kg ip, supplemented with 0.1 g/kg iv as needed), placed on a heating blanket to maintain rectal temperature at 37°C, and ventilated through a tracheal cannula (7–8 ml/kg × 72 cycles/min) with a mixture of oxygen and room air (~80–20%). The left femoral artery and vein were cannulated. The left aortic depressor nerve was carefully isolated at its junction with the superior laryngeal nerve and placed on a bipolar platinum-iridium electrode. Then the nerve-electrode preparation was embedded in silicone gel (Wacker Chemie).

Stimulation protocol. As previously described (3), the aortic nerve was stimulated with rectangular trains of impulses (2 ms, 100 Hz) delivered by a stimulator (model S88; Grass) at a fixed voltage intensity that was initially chosen to induce reproducible depressor responses of ~40 mmHg. At each modulation frequency (0.03–0.8 Hz), the nerve was stimulated during one-half cycle (16.7–0.63 s) at the beginning of each cycle. Stimulation trials lasted 4 min, except at the lowest frequency (0.03 Hz) where the nerve was stimulated for 8 min. The order of modulation frequencies was randomized, and 3–4 min of recovery were allowed between consecutive trials. The output signal of the stimulator was sampled at 2,000 Hz by the computer. All experiments were performed under total cardiac autonomic blockade (atropine methyl nitrate and atenolol, 2 mg/kg iv each, every hour) so as to avoid the distorting influence of heart rate fluctuations that could be evoked by aortic nerve stimulation (3). The complete set of modulation frequencies was applied before and after DMI administration (2 mg/kg iv).

Data analysis. At each modulation frequency, transfer function analysis between impulses delivered by the stimulator (input signal) and mean AP (output signal) was performed (8). Briefly, coherence, phase and gain were calculated using overlapped Fourier transform processing applied to consecutive 102.4-s time series (204.8 s at 0.03-Hz modulation frequency) after resampling at 10 Hz. With this analysis, at least six full cycles were contained within each period. Phase and gain were taken at the peak coherence frequency (see RESULTS, Fig. 3). The transfer function of the rat baroreflex loop shows the characteristics of a low-pass filter combined with a fixed time delay (3). Therefore, in each individual rat and for each experimental condition, phase and gain functions were submitted to nonlinear regression analysis (SYSTAT 8.0, SPSS, Chicago, IL) to estimate the characteristics of the filter and the time delay (15).

Effect of DMI on the Frequency Responses of Hindlimb Vascular Conductance to Sympathetic Stimulation in Anesthetized Rats

Surgical procedures. Rats were prepared as described above (see Effect of DMI on the Frequency Responses of Mean AP to Aortic Depressor Nerve Stimulation in Anesthetized Rats). The right carotid artery and jugular vein were cannulated. For the continuous measurement of iliac blood flow, an ultrasonic transit-time flow probe (model 1RB; Transonic Systems, Ithaca, NY) was placed around the left common iliac artery, just below the aortic bifurcation. The space between probe and vessel was filled with an acoustic couplant (H-R lubricating jelly; Carter-Wallace, New York, NY). The
Results of desipramine on mean levels and short-term variabilities of MAP and RSNA in conscious rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Desipramine</th>
</tr>
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<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>110 ± 3</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>Total power (mmHg²)</td>
<td>3.18 ± 0.35</td>
<td>7.52 ± 1.97*</td>
</tr>
<tr>
<td>LF power, mmHg²</td>
<td>1.98 ± 0.23</td>
<td>6.43 ± 1.86*</td>
</tr>
<tr>
<td>MF power, mmHg²</td>
<td>0.92 ± 0.14</td>
<td>0.50 ± 0.09*</td>
</tr>
<tr>
<td>HF power, mmHg²</td>
<td>0.28 ± 0.08</td>
<td>0.59 ± 0.14*</td>
</tr>
<tr>
<td>RSNA (µV)</td>
<td>20.6 ± 3.9</td>
<td>11.5 ± 2.6*</td>
</tr>
<tr>
<td>Total power, nu²</td>
<td>1.325 ± 433</td>
<td>393 ± 91*</td>
</tr>
<tr>
<td>LF power, nu²</td>
<td>120 ± 38</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>MF power, nu²</td>
<td>394 ± 150</td>
<td>82 ± 18*</td>
</tr>
<tr>
<td>HF power, nu²</td>
<td>814 ± 246</td>
<td>239 ± 65*</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 7). LF, low-frequency (0.005–0.269 Hz); MF, mid-frequency (0.273–0.742 Hz); HF, high-frequency (0.747–5 Hz); nu, normalized units; RSNA, renal sympathetic nerve activity; MAP, mean arterial pressure. *P < 0.05 vs. control.

Statistics

Data are presented as means ± SE. Paired comparisons used the Wilcoxon signed rank test. Differences were considered statistically significant when P < 0.05.

Results

Effect of DMI on Short-Term Variability of Mean AP and Renal SNA in Conscious Rats

As summarized in Table 1, acute DMI administration did not change the mean AP level but increased its overall variability. The latter effect was mainly due to a threefold increase in the LF component of mean AP variability. As can be seen from an individual example (Fig. 1) and from the group-average mean AP spectrum (Fig. 2), DMI strongly enhanced mean AP oscillations around 0.1 Hz. Finally, DMI reduced power in the MF band containing the Mayer waves and increased power in the HF band containing the respiration-linked oscillations.

With regard to renal SNA, it was observed that DMI decreased its mean value by ~50% and strongly depressed all frequency components of its variability, except in the LF band where the decrease did not reach statistical significance (Table 1). DMI abolished the prominent MF oscillations centered around 0.4 Hz and the HF respiration-related oscillations that were located at 1.4–1.8 Hz under control conditions (Fig. 2).

There was no enhancement of renal SNA oscillations around 0.1 Hz after DMI administration (Figs. 1 and 2).

Effect of DMI on the Frequency Responses of Mean AP to Aortic Depressor Nerve Stimulation in Anesthetized Rats

Prestimulation levels of mean AP and heart rate did not differ significantly between the experimental con-
As illustrated in Fig. 3, rhythmic aortic nerve stimulation induced regular oscillations of mean AP that were strongly attenuated after DMI. However, coherence between impulses and mean AP was close to unity in both cases, thus allowing for reliable estimation of phase and gain.

When considering average results of coherence and transfer function analyses (Fig. 4), it was observed that coherence was high (>0.9) up to 0.8 Hz under control conditions, whereas it decreased precipitously beyond 0.5 Hz after DMI administration. In this latter case, aortic nerve stimulation did not induce clear mean AP oscillations at 0.6 and 0.8 Hz. The gain functions showed a seemingly exponential decay with increasing modulation frequency. At any given frequency, gain was significantly decreased by DMI. Phase angles were positive at low modulation frequencies, indicating that impulses led mean AP with respect to the out-of-phase pattern. With increasing modulation frequency of the aortic nerve, phase angles decreased and eventually became negative. Phase came close to 0 at 0.4 and 0.2 Hz, before and after DMI, respectively. Whatever the frequency, phase angles were significantly decreased after DMI administration.

As the gain function showed the characteristics of a low-pass filter, the equations of either a first- or a second-order low-pass filter were fitted to experimental gain values after transformation $G = 20 \log_{10}(\text{gain})$, expressed in dB. In all rats and under both experimental conditions, the best fit was obtained with the equation of a second-order, low-pass filter

$$G(f) = 20 \log(K) - 10 \log\left(\frac{1}{[1 - (f/f_n)^2]^2 + 4\lambda^2(f/f_n)^2}\right)$$

where parameters $K$, $f_n$, and $\lambda$ are the static gain (mmHg/V), natural frequency (Hz), and damping coefficient, respectively. The correlation coefficients ($r^2$, observed vs. predicted values) were 0.980 ± 0.004 and 0.944 ± 0.009 before and after DMI administration, respectively. DMI significantly decreased the static gain from 21.3 ± 4.2 to 10.2 ± 3.0 mmHg/V, the natural frequency from 0.112 ± 0.008 to 0.063 ± 0.004 Hz, and the damping coefficient from 1.56 ± 0.18 to 0.65 ± 0.09 (Fig. 5).

Phase functions were also modeled using equations of either a first (equation 1)- or a second (equation 2)-order, low-pass filter containing a fixed time delay ($T_f$)

$$\phi(f) = 180 - \tan^{-1}\left(\frac{f}{f_c}\right) - 360 T_f$$  \hspace{1cm} (1)

where $f_c$ is the corner frequency (Hz).

$$\phi(f) = 180 - \tan^{-1}\left[\frac{2\lambda(f/f_n)}{1 - (f/f_n)^2}\right] - 360 T_f$$  \hspace{1cm} (2)

Under control conditions, the first-order model provided the best fit ($r^2 = 0.976 ± 0.004$). The estimated
time delay was 0.71 ± 0.03 s. After DMI administration, the second-order model provided the best fit ($r^2 = 0.976 ± 0.005$). The estimated delay was 0.62 ± 0.07 s. This value does not differ significantly from that obtained before DMI. The feedback oscillation frequency of the baroreflex loop (null phase) was significantly decreased by DMI from 0.39 ± 0.01 to 0.19 ± 0.01 Hz (Fig. 5).

**Effect of DMI on the Frequency Responses of Hindlimb Vascular Conductance to Sympathetic Stimulation in Anesthetized Rats**

As indicated in Table 2, DMI induced significant decreases in iliac blood flow (−27%) and vascular conductance (−23%). These changes were immediate and sustained across the experiment.
Rhythmic stimulation of the lumbar sympathetic chain induced oscillations of iliac blood flow that were sometimes associated with a slight tonic increase in AP but did not evoke clear oscillations of AP. As a consequence, vascular conductance displayed large regular oscillations (Fig. 6). DMI seemingly attenuated the amplitude of these oscillations.

Under control conditions, coherence between sympathetic stimulation and iliac vascular conductance was >0.9 across the whole range of modulation frequencies (Fig. 7). After DMI administration, coherence fell abruptly beyond 0.6 Hz. The gain functions peaked below 0.1 Hz and then decreased exponentially. DMI induced a significant decrease of the transfer gain at all modulation frequencies. The

Fig. 4. Coherence (A), phase (B), and gain (C) between impulses and mean arterial pressure as a function of modulation frequency of the aortic depressor nerve, before (○) and after (●) DMI administration. In the latter case, phase and gain at frequencies of 0.6 and 0.8 Hz are not shown because, in most cases, they were not associated with a significant coherence and, therefore, could not be reliably estimated. As voltage intensity differed between rats, absolute transfer gains could not be averaged. Therefore, in each rat, all gain values were normalized by the transfer gain measured at the lowest modulation frequency (0.03 Hz) under control conditions. Values are means ± SE (n = 8).

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Fig. 5. Bode plot of the oscillatory responses of MAP to aortic depressor nerve stimulation obtained before (thin lines) and after (thick lines) DMI administration in 8 rats. Functions were plotted using the mean parameters obtained from individual fitted curves (see RESULTS). Both gain functions were normalized by the average static gain estimated under control conditions. In the phase graph, the vertical dotted lines show the feedback oscillation frequency, i.e., the frequency at which phase shift between impulses and MAP becomes null. At this frequency, aortic nerve stimulation and MAP oscillations are in phase.
phase functions were positive at low modulation frequencies, indicating that impulses led vascular conductance with respect to the out-of-phase pattern. Phase angles then decreased gradually and eventually became negative. DMI did not markedly alter the phase function at low frequencies and slightly but significantly decreased phase angles starting from 0.15 Hz (Fig. 7).

The gain functions could be satisfactorily modeled using the equation of a second-order, low-pass filter (Fig. 8). The correlation coefficients were 0.975 ± 0.003 and 0.963 ± 0.015 before and after DMI, respectively. DMI significantly decreased the static gain from 1.46 ± 0.43 to 0.48 ± 0.09 ml·min⁻¹·mmHg⁻¹·V⁻¹, but did not alter the natural frequency (0.133 ± 0.004 vs. 0.126 ± 0.007 Hz, before and after DMI, respectively). The damping coefficient was significantly decreased by DMI from 0.806 ± 0.046 to 0.517 ± 0.045. In every rat after DMI administration, the damping coefficient was 1/√2, which means that the system exhibited a resonance, i.e., an amplification of oscillatory responses at a particular frequency

\[ f_R = f_n \sqrt{1 - 2\lambda^2} = 0.077 \pm 0.006 \text{ Hz} \]

which can also be seen from Fig. 8.

The equation of a second-order, low-pass filter could also be fitted to phase values (Fig. 8). Correlation coefficients were 0.982 ± 0.004 and 0.991 ± 0.001 before and after DMI, respectively. The estimated pure time delay was significantly increased by DMI from 0.38 ± 0.05 to 0.50 ± 0.02 s.

**DISCUSSION**

Our working hypothesis was that acute DMI administration would shift the feedback oscillation frequency of the baroreceptor reflex from 0.4 to 0.1 Hz, mainly as a result of an increased delay in the loop. Accordingly, this was expected to induce parallel alterations in AP and SNA variabilities, namely a shift of spectral power from 0.4 to 0.1 Hz. It was found that DMI actually abolished 0.4-Hz oscillations of renal SNA but did not enhance its variability ~0.1 Hz. Furthermore, DMI shifted the baroreflex feedback oscillation frequency from 0.4 to 0.2 Hz, and this was not due to an increased fixed time delay but rather to accentuated low-pass filter properties of the loop. Interestingly, the effects of DMI at the vascular neuroeffector junction could not explain the latter changes in the dynamic properties of the baroreceptor reflex.

In accordance with previous studies in anesthetized rats (16) and conscious humans (14) and rabbits (13), we found that acute DMI administration decreased the

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**Table 2. Effect of desipramine on prestimulation levels of cardiovascular variables in anesthetized rats**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>87 ± 3</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>348 ± 5</td>
<td>355 ± 4</td>
</tr>
<tr>
<td>IBF, ml/min</td>
<td>9.7 ± 1.2</td>
<td>7.1 ± 0.8*</td>
</tr>
<tr>
<td>IVC, ml·min⁻¹·mmHg⁻¹</td>
<td>0.113 ± 0.014</td>
<td>0.087 ± 0.009*</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 7). HR, heart rate; IBF, iliac blood flow; IVC, iliac vascular conductance. *P < 0.05 vs. control.
average level of SNA in conscious rats. The DMI-induced decrease in renal SNA was paralleled by a strong reduction of its overall variability. This observation simply reflects the redundancy existing between average levels and variance estimates of SNA, because this nerve signal is essentially constituted by intermittent bursts of varying amplitude and frequency (26).

Bursting patterns of renal SNA include cardiac cycle-related oscillations that account for a minor part of the overall spectral power, at least in resting rats (7, 11, 28). These fluctuations were not examined in this study due to the 10-Hz averaging procedure applied before spectral analysis. At lower frequencies (0.8–2 Hz), renal SNA exhibits oscillations coherent with mean AP. Mean AP oscillations at these frequencies are due to respiratory fluctuations in stroke volume (20). Under normal breathing conditions, the respiratory rhythm of sympathetic activity is most likely provided by brain stem respiratory neurons and possibly modulated by the baroreceptor reflex (29). Recent studies indicate that above 1 Hz, sympathetic oscillations

Fig. 8. Bode plot of the oscillatory responses of IVC to stimulation of the lumbar sympathetic chain obtained before (thin lines) and after (thick lines) DMI administration in 7 rats. Functions were plotted using the mean parameters obtained from individual fitted curves (see RESULTS). Both gain functions were normalized by the average static gain estimated under control conditions.

Fig. 7. Coherence (A), phase (B), and gain (C) between impulses and IVC as a function of modulation frequency of the lumbar sympathetic chain before (○) and after (●) DMI administration. In the latter case, phase and gain at the 0.8-Hz frequency are not shown, because, in most cases, coherence was too low to allow reliable estimates. In each rat, all gain values were normalized by the transfer gain measured at the lowest modulation frequency (0.03 Hz) under control conditions. Values are means ± SE (n = 7).
are not translated into oscillations of vascular resistance but rather contribute to increase vasoconstrictor tone and, hence, to sustain AP (19, 25, 31, 32). Our study indicates that the reduction of HF fluctuations of renal SNA was not accompanied by a reduction of the AP level. Data obtained in conscious rabbits suggest that the absence of depressor effect of the systemic administration of DMI is attributable to the peripheral effects of the drug, namely the blockade of NE reuptake at vascular neuroeffector junctions, because the central administration of DMI induces parallel decreases in renal SNA and mean AP (13).

Fluctuations of SNA contribute to generate fluctuations of mean AP at frequencies <1 Hz. The renal SNA spectrum shows a prominent peak centered around 0.4 Hz. We confirm that this sympathetic rhythm is tightly coupled with AP Mayer waves (5, 7). At 0.4 Hz, oscillations of AP and SNA reflect both the feedforward from SNA to AP and the feedback from AP to SNA. Both mechanisms are demonstrated by the abolition of Mayer waves after either α-adrenoceptor blockade (9, 21) or sinoaortic denervation (8, 18). As baroreflex structures introduce a 180° phase lag between baroreceptor afferent activity and AP at 0.4 Hz (3), the 0.4-Hz component of any spontaneous AP perturbation will be translated into an opposite change delayed by exactly one half cycle, which in turn will induce a reflex change in the opposite direction after the same one half cycle delay. A self-sustained oscillation is thereby generated, provided that the open-loop gain of the system is >1 at the feedback oscillation frequency (15). The disappearance of the 0.4-Hz rhythm in renal SNA after DMI administration is consistent with the hypothesis that DMI interferes with the dynamic properties of the baroreceptor reflex, namely its feedback oscillation frequency and/or its dynamic gain at 0.4 Hz. At frequencies <0.2 Hz, coherence between mean AP and renal SNA tends to fall. Low coherence points either to a nonlinear relation (7) or to an absence of coupling. However, the selective increase in the LF components of AP variability after either chemical sympathectomy or sinoaortic denervation (8, 9) suggests that the sympathetic limb of the baroreceptor reflex exerts a powerful stabilizing influence on AP in this frequency band. After DMI administration, there was a strong enhancement of LF oscillations of mean AP, especially around 0.1 Hz. The lack of a parallel increase in renal SNA fluctuations at this frequency argues against a direct role of SNA in generating these AP oscillations. However, we previously showed that α-adrenoceptor blockade almost completely abolishes the DMI-induced AP oscillations at 0.1 Hz (4). This would suggest that SNA plays at least a permissive role in the genesis of these oscillations. Such a permissive role of adrenergic vasoconstrictor tone has indeed been suggested in the generation of a major slow (0.1–0.15 Hz) oscillation in the mesenteric circulation of conscious rats (23). Overall, the finding of an increased variability of AP at low frequencies in the absence of a concomitant increase in renal SNA variability points to a decreased effectiveness of the sympathetic component of the baroreceptor reflex in buffering AP fluctuations at these frequencies.

The dynamic properties of the baroreceptor reflex were studied by determining the frequency responses of AP to baroreceptor afferent stimulation in anesthetized rats. Because autonomic influences on the heart had been blocked and because we previously showed that AP responses to aortic nerve stimulation are abolished by ganglionic blockade (3), it seems logical to propose that this method only examines the sympathetic vascular component of the baroreceptor reflex. To determine the characteristics of the transfer function from aortic nerve stimulation to mean AP, we fitted equations of low-pass filters to experimental gain and phase values. Under control conditions, the gain function was satisfactorily approximated to that of an overdamped second-order, low-pass filter. Within the limited frequency range that was investigated, the gain function of such a system resembles that of a first-order, low-pass filter, which had been found in our previous modeling study by using linear regression analysis (3). DMI had three main effects on the gain function of the baroreceptor reflex. First, it decreased the static gain, which was also confirmed by the attenuation of the steady-state responses to step stimulation of the aortic nerve (data not shown). Such an effect is in keeping with the previous observation that both central and systemic administration of DMI in conscious rabbits moves the set point of the mean AP-renal SNA relationship toward its lower plateau (12) so that there is less room left for sympathoinhibition. Second, DMI almost halved the natural frequency of the low-pass filter. Third, it significantly decreased the damping coefficient of the filter. These two latter effects had profound consequences on the phase function between aortic nerve stimulation and mean AP. The phase function showed a much steeper decrease at low frequencies after DMI administration than in control conditions. These accentuated low-pass filter properties were entirely responsible for the shift of the feedback oscillation frequency from 0.4 to 0.2 Hz, because there was no significant change in the fixed time delay. The DMI-induced abolition of 0.4-Hz oscillations in both mean AP and renal SNA is consistent with the lowering of the feedback oscillation frequency of the baroreflex loop. At the new frequency of 0.2 Hz, there was no feedback oscillation in mean AP and renal SNA, probably because the dynamic gain at this frequency was not high enough to allow for a self-sustained oscillation. The DMI-induced enhancement of 0.1-Hz oscillations of mean AP is also consistent with the depressed baroreflex transfer gain at this frequency. The residual coherence between renal SNA and mean AP observed ~0.1 Hz probably reflects baroreflex operation.

The overall transfer function of the baroreceptor reflex has been reported to combine the transfer properties of the so-called neural arc (from AP to SNA) and those of the so-called peripheral arc (from SNA to AP) (17). Any drug-induced alteration in the overall baroreflex transfer properties could therefore result from a change in either transfer function. Considering the
major role of NE reuptake in terminating the effect of neurally released NE (22), we anticipated that DMI would induce marked changes in the transfer properties of the resistance vasculature. In the present study, we examined the effects of DMI on the transfer function from sympathetic stimulation to vascular conductance in the iliac vascular bed. This circulation was chosen because it has been shown to be particularly sensitive to baroreflex influences (24) and thus is probably a major effector in baroreflex adjustments of total peripheral resistance. Under control conditions, the transfer properties of the iliac vasculature showed the characteristics of a second-order, low-pass filter, which is in accordance with previous observations (30). The fixed time delay of the response was ~0.4 s, which is in good agreement with the delay between a change in renal SNA and a parallel change in AP, as could be estimated by a time-domain method in conscious rats (6). DMI induced a slight tonic vasoconstriction in the iliac circulation, which was possibly mediated by increased plasma NE concentrations secondary to neuronal uptake blockade (13). The static gain of the transfer function was strongly decreased by DMI, as were the steady-state responses to step stimulation of the lumbar chain (data not shown). It is likely that DMI decreases the amount of NE released per nerve impulse, secondary to overstimulation of presynaptic α2-adrenoceptors by raised intrasynaptic concentrations of NE (13). This inhibitory effect is probably more important in the hindlimb circulation than in other regional circulations, because DMI has been reported to enhance pressor responses to sympathetic nerve stimulation in the pithed rat (2). DMI did not change the natural frequency of the low-pass filter and only slightly increased the fixed time delay. These observations largely invalidate our working hypothesis that the removal rate of NE via neuronal reuptake is the frequency-limiting step in the vascular response to sympathetic modulation, at least in the hindlimb circulation. In this respect, the vascular neuroeffector junction differs from the neuroeffector junction of the sinus node. Recently, it was indeed reported that DMI accentuates the low-pass filter characteristics and markedly prolongs the time delay of the heart rate response to sympathetic stimulation (27). One interesting finding is that DMI decreased the damping coefficient of the low-pass filter to such an extent that a resonance frequency near 0.1 Hz could be discerned. Such a behavior of the resistance vessels, if present in several regional circulations, might well favor the appearance of a spontaneous AP oscillation at 0.1 Hz.

Perspectives

The present study indicates that NE reuptake blockade with DMI attenuates and slows baroreflex responses without increasing the fixed time delay in the loop. These effects are responsible for the disappearance of Mayer waves and contribute to increase AP variability at low frequencies. The lack of a major effect of DMI on the transfer properties of the resistance vasculature together with its strong depressant effect on renal SNA variability suggest that DMI acts on barosensitive structures controlling SNA in the central nervous system. It therefore remains to be determined whether DMI alters the transfer properties of the neural arc of the baroreceptor reflex.

REFERENCES


