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Effect of desipramine on spontaneous arterial pressure oscillations in the rat

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Abstract

There has been no previous report on the effect of the noradrenaline uptake inhibitor desipramine on short-term variability of arterial pressure. Mean arterial pressure was recorded in 9 conscious resting rats during 4 consecutive 30-min periods: (1) under baseline conditions, (2) after desipramine administration (2 mg/kg i.v., followed by 1 mg/kg every hour), then after (3) cardiac autonomic blockade with methylatropine and atenolol, and (4) α-adrenoceptor blockade with phentolamine. Fast Fourier transform analysis was applied to beat-to-beat data after resampling at 10 Hz of consecutive 205-s time series. Desipramine did not change the mean level and overall variability of mean arterial pressure. However, spectral power in the mid-frequency (0.3–0.5 Hz) band containing the Mayer waves was reduced by more than 80%, and power in the low-frequency (0.05–0.2 Hz) band was enhanced by approximately 50%, especially due to the appearance of a major oscillation centred at 0.095 ± 0.005 Hz. This slow oscillation was further enhanced after cardiac autonomic blockade and was abolished after α-adrenoceptor blockade. In conclusion, desipramine profoundly alters short-term arterial pressure variability in resting rats, mainly by shifting vasomotor waves from 0.4 to 0.1 Hz. Desipramine may prove a valuable pharmacological tool to study the dynamic aspects of arterial pressure control.

Keywords: Arterial pressure variability; Desipramine; Mayer wave; Spectral analysis; Rat, conscious

1. Introduction

The effects of desipramine on the steady-state levels of cardiovascular variables are well documented. In humans (Esler et al., 1991) and laboratory animals (Cohen et al., 1990; Eisenhofer et al., 1991; Lavian et al., 1991; Huangfu et al., 1995), the acute systemic administration of desipramine has consistently been observed to induce decreases in sympathetic nervous activity with little or no change in the mean level of arterial pressure, at least in conscious subjects (Eisenhofer et al., 1991; Esler et al., 1991; Tella et al., 1993). The mechanism of the sympathoinhibition probably involves overstimulation of α_2-adrenoceptors in the brain stem (Cohen et al., 1990; Lavian et al., 1991; Huangfu et al., 1995), possibly as a consequence of noradrenaline uptake inhibition. The common interpretation for the lack of depressor effect of desipramine is that blockade of noradrenaline uptake at vascular neuroeffector junctions compensates for the decreased firing rate of sympathetic neurons (Eisenhofer et al., 1991; Esler et al., 1991).

In contrast, little is known about the effects of desipramine on the reflex control of arterial pressure. It has been shown in conscious rabbits that desipramine induces a substantial attenuation of the renal sympathetic baroreflex with minimal change in the cardiac baroreflex (Dorward et al., 1991). Theoretically, both the central and peripheral actions of desipramine would be expected to alter the dynamic control of arterial pressure. Such an alteration is indeed suggested by the frequent occurrence of postural hypotension as a side effect of treatment with tricyclic antidepressant drugs (Jefferson, 1989).

The aim of the present study was to examine the effects of acute desipramine administration on the short-term variability of arterial pressure in normotensive rats. Changes in arterial pressure variability were assessed by computing power spectra of mean arterial pressure collected over 30-min periods before and after administration of desipramine. In desipramine-pretreated rats, total cardiac autonomic blockade was performed to assess the role of cardiac vs. vascular factors in causing spontaneous arterial

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pressure fluctuations. Finally, phentolamine was administered to determine whether the effects of desipramine on arterial pressure variability were mediated by α-adrenoceptor modulation.

2. Materials and methods

2.1. Animals and surgery

Experiments were performed on male Sprague–Dawley rats weighing 300–350 g (Iffa-Credo, L'Arbresle, France). Animals were housed under a 12 h (0800–2000 h) light–dark cycle and had free access to a standard rat chow (Usine d'Alimentation Rationnelle, Villemoisson s/Orge, France) and tap water.

Rats were anaesthetized with halothane (1.5–2% in oxygen) and femoral arterial and venous catheters were inserted into the distal abdominal aorta and inferior vena cava for arterial pressure measurement and drugs administration, respectively (Zhang et al., 1995). Catheters were exteriorized at the interscapular region. The whole surgical procedure lasted 20–30 min. Each rat was then placed in a large individual recording cage and was allowed two days to recover from surgery.

2.2. Experimental protocol

Experiments were performed on conscious freely moving rats accustomed to the recording environment. The arterial catheter was connected to a pre-calibrated pressure transducer (TNF-R; Ohmeda, Bilthoven, The Netherlands) through a two-way stopcock, which allowed the continuous infusion of a heparinized 5% glucose solution (0.4 ml/h). The arterial pressure signal was fed simultaneously to an amplifier-recorder (Model 8802; Gould, Cleveland, OH, USA) and to a personal computer equipped with an A/D converter board (AT-MIO-16; National Instruments, Austin, TX, USA). Using LabVIEW 4.0 software (National Instruments), the arterial pressure curve was sampled at 500 Hz.

The recording session consisted of 4 consecutive 1-h periods. The baseline period was initiated when the animals were quiet and cardiovascular variables had stabilized. Then, desipramine HCl was administered as an i.v. bolus injection (2 mg/kg), followed by 1 mg/kg every hour. Pilot experiments indicated that these doses were sufficient to achieve an almost complete and stable inhibition of noradrenaline uptake over 1-h periods. However, the effectiveness of blockade was verified in each rat by comparing the pressor responses to tyramine HCl (250 μg/kg i.v.) before and 1 h after each administration of desipramine. Tyramine releases noradrenaline from its endogenous stores after being taken up by sympathetic nerve terminals through a desipramine sensitive mechanism (Bonaccorsi and Garattini, 1966). Total cardiac autonomic blockade was achieved by the combined i.v. administration of atropine methyl nitrate and atenolol (2 mg/kg each, every hour), as previously described (Bertram et al., 1998). Then, rats received a single i.v. administration of the non selective α-adrenoceptor antagonist phentolamine HCl (5 mg/kg), which dose has been shown to completely abolish pressor responses to phenylephrine HCl (3 μg/kg i.v.) for at least 1 h (Lo et al., 1991).

In an additional group of rats, the same protocol was carried out except that saline instead of desipramine was administered before cardiac autonomic blockade and phentolamine administration.

All drugs were obtained from Sigma-Aldrich Chimie (Saint Quentin Fallavier, France).

2.3. Data analysis

Arterial pressure time series were processed off-line on a work station (SPARC 1; Sun Microsystems, Mountain View, CA, USA). For each cardiac cycle, the computer calculated mean arterial pressure and heart rate. From each 1-h recording period corresponding to the 4 different experimental conditions, a 30-min period during which the rat was quiet and displayed minimal activity was selected for spectral analysis. The 5-min period immediately following an injection was always discarded. After phentolamine administration, the 30-min period used for analysis was taken after arterial pressure had partly recovered and reached a new stable level, usually within 15 min after the injection.

Power spectral analysis was performed as previously described (Létienne et al., 1998). In brief, discrete time series of mean arterial pressure and heart rate values were generated from beat-to-beat data after linear interpolation and equidistant sampling at 10 Hz. For a 30-min recording period, 16 data sets of 2048 points (204.8 s) overlapping by half were processed. The frequency resolution was therefore 0.005 Hz. Data sets with standard deviations outside the 95% confidence interval for the total recording period were discarded. In each set, the linear trend was removed and a Hanning window was applied. Power spectral density was calculated using a fast Fourier transform algorithm. Spectra obtained for the different data sets were averaged. The low-frequency band was defined from 0.05 to 0.2 Hz and the mid-frequency band from 0.3 to 0.5 Hz. Total (from 0 to 5 Hz, referred to as overall variability), low-frequency and mid-frequency spectral powers were calculated by integration.

Coherence analysis between mean arterial pressure and heart rate was performed, with mean arterial pressure as the input signal and heart rate as the output signal (Cerutti et al., 1994). This analysis provided a squared coherence function, ranging from 0 to 1. Coherence was considered significant when > 0.3 (Benignus, 1969). Because cardiac autonomic blockade almost abolished heart rate variability (see Results), coherence analysis was performed over the two recording periods obtained before autonomic blockade. The transfer function between mean arterial pressure

and heart rate was not calculated, as phase and gain cannot be safely interpreted in a closed-loop system (Kawada et al., 1997).

2.4. Statistics

Results are presented as the mean ± S.E.M. Differences between experimental conditions were evaluated by means of one-way analysis of variance for repeated measures followed by Fisher's test.

3. Results

3.1. Effect of desipramine on mean values and overall variabilities of mean arterial pressure and heart rate

The first i.v. dose of desipramine did not induce any significant change in the mean values of mean arterial pressure and heart rate (Table 1), although a slight, transient pressor effect was observed in some rats just after the desipramine injection. Tyramine administration elicited pressor responses under baseline conditions (peak change in mean arterial pressure, 53 ± 2 mm Hg) which were strongly attenuated 1 h after desipramine administration (9 ± 2 mm Hg). Subsequent cardiac autonomic blockade did not induce significant changes in the mean levels of mean arterial pressure and heart rate. Tyramine administration at the end of this recording period, i.e., 1 h after the second desipramine administration, increased mean arterial pressure by 6 ± 4 mm Hg, which does not differ significantly from the response measured before autonomic blockade. Finally, α-adrenoceptor blockade with phentolamine decreased mean arterial pressure by ~20 mm Hg without altering the mean heart rate level.

Considering overall variabilities, it was observed that desipramine alone did not alter mean arterial pressure and

Table 1
Effects of desipramine, alone and in combination with cardiac autonomic blockade and α-adrenoceptor blockade, on mean levels and short-term variabilities of mean arterial pressure and heart rate in conscious rats
Values are means ± S.E.M. ($n = 9$ rats).
DMI, desipramine; CAB, cardiac autonomic blockade; P, phentolamine; MAP, mean arterial pressure; HR, heart rate; LF, low-frequency (0.05–0.2 Hz); MF, mid-frequency (0.3–0.5 Hz).

	Baseline	DMI	DMI + CAB	DMI + CAB + P
MAP				
Mean (mm Hg)	115 ± 2	117 ± 3	119 ± 3	100 ± 2[a,b,c]
Total power (mm Hg^2)	5.97 ± 0.88	5.57 ± 0.46	9.37 ± 0.74[a,b]	2.08 ± 0.16[a,b,c]
LF power (mm Hg^2)	2.11 ± 0.30	3.15 ± 0.24[a]	4.27 ± 0.58[a,b]	0.70 ± 0.08[a,b,c]
MF power (mm Hg^2)	1.18 ± 0.14	0.19 ± 0.02[a]	0.27 ± 0.05[a]	0.24 ± 0.03[a]
HR				
Mean (b.p.m.)	361 ± 12	349 ± 14	376 ± 10	375 ± 14
Total power (b.p.m.^{2})	49.2 ± 10.5	54.9 ± 10.9	5.54 ± 1.09[a,b]	5.67 ± 0.80[a,b]
LF power (b.p.m.^{2})	11.1 ± 2.1	18.1 ± 4.6[a]	0.36 ± 0.08[a,b]	0.11 ± 0.02[a,b]
MF power (b.p.m.^{2})	1.00 ± 0.24	1.07 ± 0.26	0.15 ± 0.04[a,b]	0.07 ± 0.02[a,b]

[a] $P < 0.05$ compared with Baseline; [b] $P < 0.05$ compared with DMI; [c] $P < 0.05$ compared with DMI + CAB.

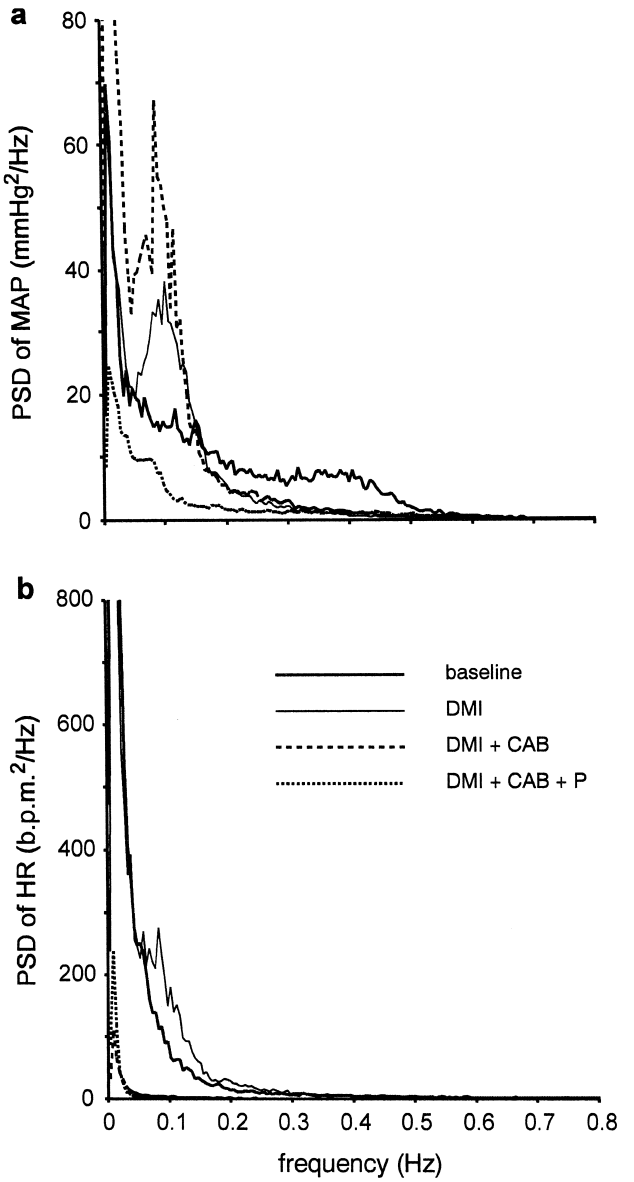

Fig. 1. Average power spectra of (a) mean arterial pressure (MAP) and (b) heart rate (HR) computed from 30-min beat-to-beat recordings in 9 conscious rats under baseline conditions, after desipramine (DMI) administration, after desipramine combined with cardiac autonomic blockade (CAB), and after additional α-adrenoceptor blockade with phentolamine (P). As desipramine did not affect the respiration-linked high-frequency (> 1 Hz) oscillations of mean arterial pressure, only the frequency range of interest is shown. Standard errors have been omitted for clarity. PSD, power spectral density.

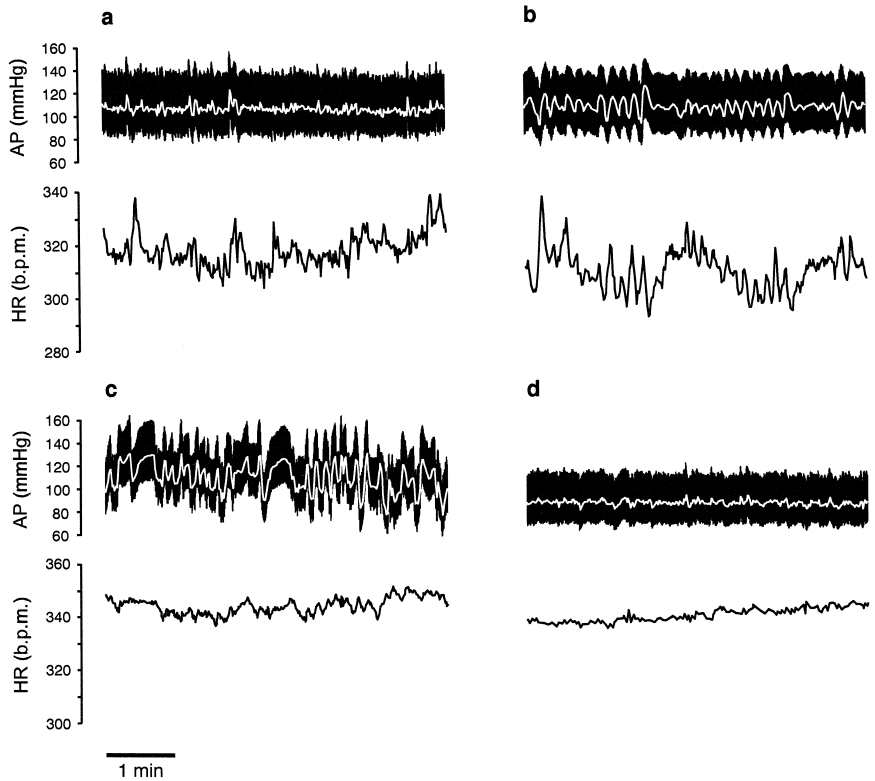

Fig. 2. Original 5-min recordings of pulsatile arterial pressure (AP), mean arterial pressure (white trace) and heart rate (HR) obtained in a conscious resting rat (a) under baseline conditions, (b) after desipramine administration, (c) after desipramine combined with cardiac autonomic blockade, and (d) after additional α-adrenoceptor blockade with phentolamine.

heart rate variabilities (Table 1). Subsequent cardiac autonomic blockade induced a significant increase in mean arterial pressure variability and almost abolished heart rate variability. Phentolamine decreased mean arterial pressure variability without inducing a further change in heart rate variability.

3.2. Effect of desipramine on the spectral profile of mean arterial pressure and heart rate variabilities

Fig. 1 summarizes the results of spectral analysis of mean arterial pressure and heart rate in the 4 experimental conditions. Arterial pressure Mayer waves, that were centred at 0.402 ± 0.007 Hz in the intact condition, completely disappeared after desipramine administration. Desipramine also induced the appearance of a clear mean arterial pressure oscillation centred at 0.095 ± 0.005 Hz, which was further enhanced after cardiac autonomic blockade, and almost abolished after phentolamine administration. Concerning heart rate variability, desipramine increased power spectral density in the low-frequency band. After cardiac autonomic blockade, either alone or combined with phentolamine, all frequency components of heart rate variability were strongly depressed. The calculation of mean arterial pressure spectral powers demonstrated a 84% reduction in the mid-frequency band containing the Mayer waves, and a 49% increase in the low-frequency band after desipramine administration (Table 1). Cardiac autonomic blockade induced a further 35% rise in mean arterial pressure low-frequency power. The

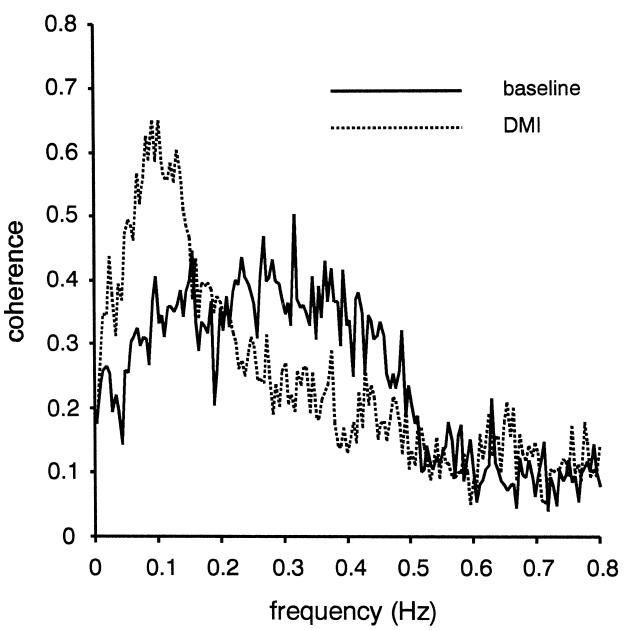

Fig. 3. Average coherence spectra computed between mean arterial pressure and heart rate in 9 conscious rats under baseline conditions and after desipramine administration. Standard errors have been omitted for clarity. As peak coherence frequencies slightly differed between rats, maximum coherence values in the average spectra are lower than the group means calculated from individual values (see text).

major effect of desipramine on heart rate variability was a 63% increase in the low-frequency power.

Fig. 2 illustrates the most obvious effect of desipramine on arterial pressure variability. Within the few minutes after desipramine administration, it was consistently observed that arterial pressure started to oscillate slowly. These oscillations were usually very regular and of moderate amplitude (~10 mm Hg), but they also showed a 'waxing-and-waning' pattern, sometimes reaching a 20-mm Hg amplitude. Meanwhile, heart rate showed seemingly opposite oscillations. After cardiac autonomic blockade, heart rate oscillations were no longer visible while arterial pressure oscillations were enhanced. Finally, phentolamine abolished the slow oscillations of arterial pressure.

3.3. Effect of desipramine on the relationships between mean arterial pressure and heart rate oscillations

Under baseline conditions, coherence between mean arterial pressure and heart rate was significant in the 0.1–0.5 Hz range (Fig. 3), and reached a maximum (0.679 ± 0.040) at 0.335 ± 0.022 Hz. After desipramine administration, coherence was no longer significant beyond 0.2 Hz and was maximum (0.772 ± 0.046) at 0.111 ± 0.013 Hz.

3.4. Effect of cardiac autonomic blockade and phentolamine administration in the absence of desipramine

In the group receiving saline instead of desipramine, the pressor responses to tyramine were stable over time (54 ± 3, 56 ± 3 and 59 ± 4 mm Hg under baseline conditions, after saline and after cardiac autonomic blockade, respectively), thus confirming that the desipramine-induced attenuation of these responses was not due to depletion of endogenous noradrenaline stores by tyramine. In the absence of desipramine, cardiac autonomic blockade did not significantly alter total, low- and mid-frequency powers of mean arterial pressure (Table 2). Subsequent α-adrenoceptor blockade with phentolamine decreased all frequency components of mean arterial pressure variability.

Table 2
Effects of sequential cardiac autonomic blockade and α-adrenoceptor blockade on mean levels and short-term variabilities of mean arterial pressure and heart rate in conscious rats
Values are means ± S.E.M. ($n = 5$ rats).
NaCl, saline; CAB, cardiac autonomic blockade; P, phentolamine; MAP, mean arterial pressure; HR, heart rate; LF, low-frequency (0.05–0.2 Hz); MF, mid-frequency (0.3–0.5 Hz).

	Baseline	NaCl	NaCl + CAB	NaCl + CAB + P
MAP				
Mean (mm Hg)	115 ± 5	112 ± 5	117 ± 5[b]	94 ± 4[a,b,c]
Total power (mm Hg^2)	5.49 ± 1.29	5.68 ± 0.82	7.12 ± 0.60	1.59 ± 0.15[a,b,c]
LF power (mm Hg^2)	2.34 ± 0.46	2.51 ± 0.41	2.30 ± 0.21	0.43 ± 0.04[a,b,c]
MF power (mm Hg^2)	0.68 ± 0.18	0.63 ± 0.16	0.93 ± 0.16	0.12 ± 0.02[a,b,c]
HR				
Mean (b.p.m.)	373 ± 11	358 ± 9	356 ± 5	326 ± 11[a,b,c]
Total power (b.p.m.^{2})	48.4 ± 4.9	43.6 ± 7.4	5.39 ± 0.73[a,b]	7.26 ± 1.51[a,b]
LF power (b.p.m.^{2})	11.7 ± 2.5	9.5 ± 0.9	0.73 ± 0.19[a,b]	0.43 ± 0.12[a,b]
MF power (b.p.m.^{2})	0.79 ± 0.18	0.59 ± 0.22	0.23 ± 0.02[a]	0.14 ± 0.03[a,b]

[a] $P < 0.05$ compared with Baseline; [b] $P < 0.05$ compared with NaCl; [c] $P < 0.05$ compared with NaCl + CAB.

4. Discussion

The findings support the conclusion that the acute inhibition of noradrenaline neuronal uptake with desipramine has a profound impact on the dynamic control of arterial pressure in rats, mainly by shifting vasomotor waves from 0.4 to 0.1 Hz.

The dose of desipramine used in the present study is well within the range of doses (0.3–4 mg/kg i.v.) at which desipramine has been shown previously to induce sympathoinhibition in anaesthetized rats (Lavian et al., 1991; Huangfu et al., 1995). In addition, this dose was sufficient to almost suppress the peripheral uptake of noradrenaline, as could be assessed from the inhibition of pressor responses to the noradrenaline releasing agent tyramine (Bonaccorsi and Garattini, 1966). Therefore, the cardiovascular effects of desipramine can be attributed to both its peripheral and central actions. Under these conditions, it was observed that in conscious rats, desipramine did not change the mean level of arterial pressure, which accords with previous studies in conscious humans (Esler et al., 1991) and rabbits (Eisenhofer et al., 1991). The overall variability of arterial pressure, estimated as the total spectral power, was unchanged after desipramine administration. It must however be stressed that in this study, the analysis of arterial pressure variability mainly concerned its harmonic components. The 30-min periods used for spectral analysis were selected from periods of rest, care being taken to minimize the influence of behaviour. A proper analysis of the effects of desipramine on overall arterial pressure variability should take into account behaviourally-coupled changes in arterial pressure, and therefore would require longer recordings including periods of activity. In addition, the spectral analysis procedure we used involves linear trend removal, which eliminates slow changes (cycle length > 200 s) and further reduces total spectral power. Therefore, it is possible that desipramine could induce changes in overall arterial pressure variability that were not detected with the present analysis.

Desipramine administration induced a striking rearrangement of arterial pressure variability in the frequency domain, namely the abolition of Mayer waves and the appearance of a major oscillation of ~0.1 Hz. The disap-

pearance of Mayer waves is consistent with the well-documented link between these oscillations and the level of sympathetic nervous activity (Malliani et al., 1991), which was presumably decreased by desipramine (Dorward et al., 1991; Esler et al., 1991; Lavian et al., 1991; Huangfu et al., 1995). It has been shown in conscious rats that Mayer waves are coupled with clear oscillations of renal sympathetic nervous activity (Brown et al., 1994). It could therefore be proposed that the effect of desipramine on these oscillations results from a direct α_2-adrenoceptor mediated depressant effect on medullary neurons involved in the generation of sympathetic tone (Allen and Guyenet, 1993). Accordingly, acute i.v. clonidine administration also depresses Mayer waves in conscious rats without changing the mean level of arterial pressure (Grichois et al., 1990). An alternative explanation would be that desipramine alters the dynamic properties of the arterial baroreceptor reflex. We have recently shown that the baroreflex loop of the rat exhibits positive feedback properties at $\sim$0.4 Hz (Bertram et al., 1998), which strongly supports the hypothesis that Mayer waves result from a resonance phenomenon in the loop (DeBoer et al., 1987). The resonance frequency is determined by the overall fixed time delay combined with the dynamic behaviour of the system (Bertram et al., 1998). As neuronal uptake is the main inactivating process of neurally released noradrenaline (Kopin et al., 1984), it is conceivable that after desipramine, reduced intrasynaptic washout of noradrenaline would induce slowing of vascular responses to sympathetic withdrawal, and thereby, increase the delay in the loop. Such an increased delay would reduce the resonance frequency. Regarding the dynamic properties of the baroreceptor reflex, it has been shown in rabbits that they combine the properties of the neural arc, which resemble those of a high-pass filter, and the properties of the peripheral (mainly vascular) arc, which resemble those of a low-pass filter (Ikeda et al., 1996). By acting at either level, desipramine could also lower the resonance frequency of the baroreceptor reflex. Interestingly, such a mechanism (increased delay together with accentuated low-pass filter properties) has been evidenced at the myocardial neuroeffector junction after inhibition of cholinesterase (Nakahara et al., 1998), which inactivates acetylcholine in the synapse.

The second major effect of desipramine is the enhancement of low-frequency power in arterial pressure spectra, especially due to oscillations located at $\sim$0.1 Hz. Interestingly, cardiac autonomic blockade further enhanced these slow oscillations. This observation indicates that heart rate fluctuations tended to limit arterial pressure oscillations at this frequency, probably through a baroreflex mechanism, which would accord with the tight coupling between arterial pressure and heart rate oscillations that was disclosed by coherence analysis. It was also observed that when α-adrenoceptor blockade was superimposed on cardiac autonomic blockade, the 0.1 Hz oscillations were abolished. Taken together, these findings suggest that the slow arterial pressure oscillations observed after desipramine administration are caused by an endogenous fluctuation of sympathetic vasomotor tone. As outlined above, it is possible that the resonance frequency of the arterial baroreceptor reflex could be shifted from 0.4 to 0.1 Hz, which would lead to the appearance of slow oscillations at the latter frequency. An alternative explanation would be that the so-called 'myogenic' oscillations of arterial pressure (0.1–0.15 Hz in rats; Janssen et al., 1995) are enhanced after desipramine administration, as a consequence of an impaired baroreflex control of sympathetic vasomotor tone. Such an impairment is suggested by the increased importance of heart rate fluctuations in stabilizing arterial pressure after desipramine. In the absence of desipramine, cardiac autonomic blockade did not increase arterial pressure variability, especially in the low-frequency band. A stabilizing role of reflex vagally-mediated changes in heart rate can be evidenced after interruption of the sympathetic control of vascular resistances, which is achieved by chemical sympathectomy (Ferrari et al., 1996). Myogenic oscillations of arterial pressure originate mainly in the mesenteric circulation (Janssen et al., 1995; Létienne et al., 1998) and, to a lesser extent, in the renal circulation (Janssen et al., 1995). We have recently shown that slow oscillations in the mesenteric blood flow are absent in guanethidine-sympathectomized rats, but are enhanced in rats with complete neurohumoral blockade combined with noradrenaline infusion (Létienne et al., 1998). Both observations suggest that α-adrenoceptor mediated vasoconstriction plays a permissive role in the genesis of these slow oscillations. This would accord with the observation that phentolamine reduced the low-frequency component of arterial pressure variability both in the absence and in the presence of desipramine.

In summary, this study demonstrates that desipramine is a valuable tool to explore the mechanisms governing spontaneous short-term arterial pressure variability in rats. The desipramine-induced changes in arterial pressure variability are stongly suggestive of alterations in the baroreflex control of sympathetic vasomotor tone. The shift of arterial pressure spectral power from 0.4 to 0.1 Hz could reflect a decrease in the resonance frequency of the arterial baroreceptor reflex and/or an attenuation of its dynamic gain. Both hypotheses are amenable to experimental testing.

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