ORIGINAL ARTICLE

The effect of arginine vasopressin on endothelin production in the human forearm vascular bed

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ABSTRACT

Objectives: To study whether arginine vasopressin (AVP) can stimulate endothelin production and/or release *in vivo*, in the human forearm vasculature.
Design: The effect of the infusion of AVP into the brachial artery on endothelin production across the human forearm vascular bed was studied in healthy male volunteers, and was compared with intra-arterial infusion of placebo. In another group the effects of AVP on endothelin production were studied after a prior infusion of L-N^G-monomethyl-arginine (L-NMMA), a nitric oxide-synthase inhibitor. In a fourth group the effect of L-NMMA alone, without AVP infusion, on endothelin production was studied.
Methods: We measured the effects of AVP, placebo, L-NMMA followed by AVP and L-NMMA followed by placebo on arterial and venous endothelin concentrations in the forearm of four groups, each consisting of five healthy male volunteers. Forearm blood flow was measured by strain gauge plethysmography. The endothelin production was calculated as forearm blood flow times (venous - arterial) endothelin concentration.
Results: The group infused with L-NMMA followed by infusion of 8 ng AVP/min per dl forearm volume showed a significant rise in endothelin production from 1.3 (1.8) to 5.0 (2.0) pg/min/dl at 15 minutes (p<0.05, ANOVA). This rise in endothelin production was also significantly different from the endothelin production at 15 minutes in the other three groups (p<0.01, ANOVA).
Conclusion: In healthy male volunteers intra-arterial infusion of AVP induced a rise in endothelin production in the forearm within 15 minutes, but only after

prior infusion of L-NMMA. This observation suggests that the AVP-induced production of nitric oxide offsets AVP-mediated release of endothelin.

KEYWORDS

Arginine vasopressin, endothelin, forearm, human, L-N^G-monomethyl-arginine

INTRODUCTION

Endothelin is a potent vasoconstrictive factor mainly derived from endothelial cells. The production of endothelin is regulated *in vitro* and *in vivo* by a variety of hormones, other vasoactive substances and conditions of vascular stress.[1] In human disease states, endothelin plays a role in disorders related to the vascular system such as myocardial infarction and congestive heart failure, postischaemic renal failure and in preeclampsia.[1-5] There is as yet no convincing evidence that endothelin has a role in the aetiology of essential hypertension.[6,7] Although there has been a rapid increase in knowledge of the importance of endothelin in the pathophysiology of vascular diseases, much remains to be clarified. Studies of the dynamic regulation of endothelin *in vivo* in humans have been reported, but most of these studies were hampered by the fact that only endothelin concentrations were measured and not its production, and also that the

stimulus was mostly accomplished by physical means that can possibly lead to a cascade of endothelial reactions caused by mechanical factors.[8-10] To study endothelin regulation *in vivo* in humans, a humoral factor modulating this process would be more appropriate.

Many *in vitro* experiments have shown that endothelin production can be stimulated strongly by arginine vaso-pressin (AVP), and this vasoactive agent can be used *in vivo* in humans.[11-16] Stimulation of endothelin production by AVP is mediated by the V_1 receptor.[11,12] AVP also stimulates nitric oxide (NO). This stimulation is mediated by the V_2 receptor.[17] NO in turn inhibits endothelin production.[18-20] NO synthesis can be inhibited by L-N^G-monomethyl-arginine (L-NMMA), a NO-synthase inhibitor.

With these data as a basis we set up a study to investigate endothelin production responses to intra-arterial AVP administration alone and AVP together with L-NMMA. Recent studies have made it clear that storage granules containing endothelin-1 are present in endothelial cells that can be degranulated by a number of chemical and mechanical stimuli.[21-25] A confirmation of this mechanism was reported recently in DOCA-salt hypertensive rats.[26] *In vivo* studies in humans suggested a possible rise in endothelin production five minutes after a stimulus.[8,9] The time needed before endothelin production *in vivo* in humans increases is thus uncertain so we studied endo-thelin production reactions for a period of 180 minutes. We did so in the human forearm model in male volunteers only, as sex hormones can influence endothelin levels relative to the menstrual cycle.[27]

METHODS

Approval for the study protocol was given by the local ethics committee of the Radboud University Nijmegen Medical Centre. All subjects gave informed consent. Twenty healthy nonsmoking male volunteers participated in the study. After an overnight rest and breakfast in the early morning, the experiments were performed in the afternoon, starting at 13.00 hours. During the 24 hours preceding the experiment, subjects did not consume caffeine- or alcohol-containing drinks or food, nor did they take any medication. They were also not allowed vigorous exercise on the two days preceding the test. The subjects were in a supine position during the study in a quiet room with a constant temperature of 20°C. The brachial artery of the left arm was cannulated. A deep venous catheter was introduced in the antecubital region of the same arm. Experiments started after an equilibration period of 30 minutes. Forearm blood flow (FBF) of both arms was measured by venous occlusion mercury-in-silastic strain gauge plethysmography. To obtain the mean FBF it was measured six times and averaged. Blood pressure

and heart rate were recorded intra-arterially (Hewlett-Packard, GmbH, Böblingen, FRG) (the average of six measurements). Arterial and venous blood samples were drawn at 0, 5, 15, 60, 120 and 180 minutes. We used a radioimmunoassay kit (Nichols Institute, Wijchen, the Netherlands) following C_{18} extraction for the quantitative determination of endothelin levels in plasma.[5] The anti-serum showed 67% cross-reaction with endothelin-2 and 84% with endothelin-3. Endothelin production was calculated as FBF times (venous - arterial) endothelin concentration. AVP (Pitressin, Parke Davis, Berlin) 0.05 g/l was diluted with NaCl 0.9%. AVP was infused into the brachial artery for 180 minutes at a dose of 8 ng/min per dl of forearm volume, which was determined by water displacement. L-NMMA was dissolved in NaCl 0.9% and administered for 15 minutes in a dose of 30 mg intra-arterially, preceding the AVP or placebo infusions. NaCl 0.9% was used as placebo infusion. All drugs were infused by an automatic syringe infusion pump. The levels of AVP were calculated because it was not feasible to introduce a second arterial line to draw blood for arterial AVP levels. The AVP levels were calculated as follows: 8 ng/min/dl divided by the flow in ml/min/dl times 0.6 (1-haematocrit) gives the plasma AVP levels in ng/ml. The experiments were done in four groups of five subjects. The first group was infused with 8 ng/min/dl forearm volume (FAV) of AVP for 180 minutes. The second group was infused with L-NMMA for 15 minutes followed by the same dose of AVP for 180 minutes. The third group was infused with placebo only for 180 minutes. A fourth group was infused with L-NMMA for 15 minutes followed by infusion of placebo for 60 minutes.

Statistical analysis
ANOVA tests were used to compare the effects of AVP, L-NMMA and AVP, placebo and L-NMMA and placebo on endothelin production. AVP concentrations between groups were also compared by ANOVA. Changes in BP, FBF and the changes in venous and arterial endothelin concentrations were assessed by ANOVA and if appropriate Student's t-test. In case of non-Gaussian distribution signed-rank tests were used. Statistical significance was set at two-tailed p<0.05. The Bonferroni correction for multiple comparisons was used when appropriate.

RESULTS

No differences in clinical parameters were evident between the four groups of subjects (*table 1*). After the first set of experiments, including the infusion of AVP alone, the infusion of AVP after prior L-NMMA infusion and the placebo infusion, measurements of endothelin at 120 and 180 minutes were skipped in the group infused

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Table 1 *Clinical data of the study subjects by infusion group (mean ± SD are given)*

Group	Age (years)	Body mass index (kg/m²)	Forearm volume (litre)
AVP	23.3 ± 3.0	22.2 ± 2.4	1.1 ± 0.2
L-NMMA + AVP	23.3 ± 2.9	22.8 ± 1.5	1.1 ± 0.1
Placebo	23.8 ± 2.9	23.4 ± 1.7	1.1 ± 0.1
L-NMMA + placebo	24.6 ± 3.5	22.0 ± 0.6	1.1 ± 0.3

AVP = arginine vasopressin; L-NMMA = L-N^G-mono-methyl-arginine.

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with L-NMMA followed by placebo, since no changes in endothelin levels at these time points were detected. Thus, only the results until 60 minutes for all experiments are given. The computed plasma AVP levels were in the range of 0.7 to 6 ng/ml (*table 2*). The AVP levels between the AVP group and the AVP + L-NMMA group were not significantly different (*table 2*). Also within groups the AVP levels were not significantly different.

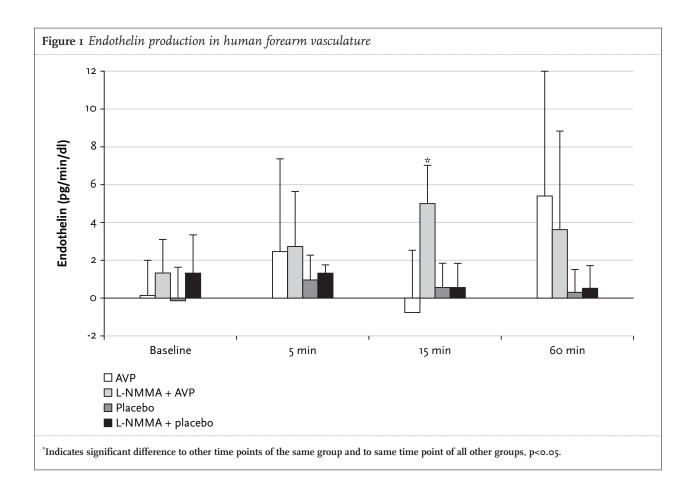The FBF in the AVP group was 4.1 (0.6) ml/min/dl at baseline, 5.4 (2.0) ml/min/dl at 15 minutes and 3.8 (1.3) at 60 minutes (p>0.05) (*table 3*). The flow in the contralateral arm did not show any significant changes either, suggesting that local infusion had not resulted in systemic effects. The mean arterial pressure (MAP) was 72.6 (6.4) at baseline and 72.3 (8.4) mmHg at 60 minutes (*table 3*). Administration of 8 ng AVP/min/dl alone for 60 minutes revealed no significant effect on endothelin production (*table 4, figure 1*).

Table 2 *Arterial and venous endothelin levels and AVP levels (mean ± SD)*

Group	Baseline	5 minutes	15 minutes	60 minutes
Arterial/venous endothelin levels (pg/ml)				
- AVP	2.6(1.1)/2.7(1.0)	3.3(1.4)/3.9(0.8)	4.5(1.5)/4.1 (1.1)	4.0(1.4)/5.0 (2.0)
- L-NMMA + AVP	2.6(1.2)/3.1(1.0)	3.0(0.7)/3.7(0.9)	3.1(1.0)/4.4 (0.8)	4.2(1.5)/4.5 (1.3)
- Placebo	2.6(0.9)/2.6(0.4)	2.5(0.8)/3.0(0.7)	2.8(0.8)/2.7 (1.5)	2.8(0.7)/3.0 (0.5)
- L-NMMA + placebo	1.8(0.6)/2.4(0.9)	1.6(0.4)/2.5(0.5)	2.2(0.8)/2.4 (0.6)	2.2(0.4)/2.8 (1.1)
Computed AVP levels (ng/ml)				
- AVP	1.2 (0.19)	1.3 (0.37)	1.1 (0.30)	1.5 (0.37)
- L-NMMA + AVP	2.2 (0.57)	1.5 (0.33)	1.2 (0.28)	1.6 (0.55)

AVP = arginine vasopressin; L-NMMA = L-N^G-mono-methyl-arginine.

Table 3 *Forearm blood flow and mean arterial pressure (mean ± SD)*

Group	Baseline	5 minutes	15 minutes	60 minutes
Forearm blood flow, experimental arm (ml/min/dl)				
- AVP	4.1 (0.6)	4.7 (2.1)	5.4 (2.0)	3.8 (1.3)
- L-NMMA + AVP	2.1 (0.7)	3.6 (1.0)	4.6 (1.4)	3.6 (1.1)
- Placebo	1.8 (0.6)	1.6 (0.4)	1.5 (0.5)	1.3 (0.5)
- L-NMMA + placebo	1.7 (0.9)	1.5 (0.6)	1.6 (0.6)	1.7 (0.7)
Mean arterial pressure (mmHg)				
- AVP	72.6 (6.4)	76.8 (6.8)	74.4 (7.2)	72.3 (8.4)
- L-NMMA + AVP	87.0 (7.5)	81.9 (7.1)	76.5 (5.6)	75.8 (5.1)
- Placebo	78.3 (6.9)	77.7 (8.7)	80.5 (7.7)	83.0 (8.2)
- L-NMMA + placebo	87.1 (4.7)	87.1 (5.3)	87.6 (3.5)	89.6 (4.1)

AVP = arginine vasopressin; L-NMMA = L-N^G-mono-methyl-arginine.

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Table 4 *Endothelin production (pg/min/dl) (mean ± SD) in the four groups in 60 minutes*

Group	Baseline	5 minutes	15 minutes	60 minutes
AVP	0.0 ± 1.8	2.4 ± 4.9	- 0.8 ± 4.1	5.4 ± 6.6
L-NMMA + AVP	1.3 ± 1.8	2.7 ± 2.9	5.0 ± 2.0*	3.6 ± 5.2
Placebo	-0.2 ± 1.6	0.9 ± 0.7	0.5 ± 1.2	0.3 ± 1.2
L-NMMA + placebo	1.3 ± 2.0	1.3 ± 0.4	0.5 ± 1.1	0.5 ± 1.2

AVP = arginine vasopressin; L-NMMA = L-N^G-mono-methyl-arginine. *Indicates significant difference compared with values in the same group p<0.05 and compared with all other groups p<0.01 (ANOVA repeated measures).

Figure 1 *Endothelin production in human forearm vasculature*

*Indicates significant difference to other time points of the same group and to same time point of all other groups, p<0.05.

The group infused with L-NMMA preceding the infusion of AVP showed a significant rise in endothelin production from baseline 1.3 (1.8) to 5.0 (2.0) pg/min/dl at 15 minutes (p<0.05) (*table 4, figure 1*). This peak in endothelin production was also significantly different from the endothelin production, at this point in all other groups (p<0.01) (*table 4*). The FBF decreased from 4.0 (1.7) at the start of the infusion of L-NMMA to 2.1 (0.7) ml/min /dl 15 minutes thereafter. Subsequently, the FBF increased from 2.1 (0.7) at baseline to 3.6 (1.0) and 4.6 (1.4) ml/min/dl at 5 and 15 minutes, respectively. After this it stabilised at 3.6 (1.1) ml/min/dl at 60 minutes (*table 3*). In the contralateral arm there were no significant changes in flow either.

The arteriovenous difference in endothelin levels showed a nonsignificant rise from 0.5 (0.8) pg/ml at baseline to 1.3 (0.6) pg/ml at 15 minutes (*table 3*). The MAP did not change significantly in this group (*table 3*).
There were no significant changes in endothelin production in the group that was infused with L-NMMA for 15 minutes followed by placebo for 60 minutes (*table 4*). The FBF decreased, but not significantly, from 3.3 (2.2) to 1.7 (0.9) after infusion of L-NMMA, and no change was seen after the subsequent placebo infusion. The contralateral arm did not show any significant changes either.
The MAP showed no changes in this group (*table 3*). The single infusion of placebo for 60 minutes did not result in significant changes in endothelin production (*table 4*).

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The FBF remained unchanged at both arms. The MAP showed a nonsignificant increase from 78.3 (6.9) at baseline to 83.0 (8.2) mmHg at 60 minutes (*table 3*).

DISCUSSION

In the present study we found that intra-arterial infusion of AVP after preceding infusion of L-NMMA can cause a rise in endothelin production in the forearm of healthy male volunteers.

The effect of AVP on endothelin production has been studied extensively *in vitro*. It has been established that AVP is involved in the mechanism of endothelin-1 immunoreactivity release through activation of protein kinase C and mobilisation of intracellular Ca^{2+} resulting from the common receptor-mediated phosphoinositol breakdown in endothelial cells.[11,12] In *in vitro* experiments, both in animal and human cell cultures, endothelin production could be stimulated with an AVP concentration of 10^{-10} M. Dose-dependent increases in endothelin production could be established with increasing concentrations of AVP up to 10^{-6} M and 10^{-5} M.[13-15]

The optimal AVP concentration to stimulate endothelin production, as deducted from these *in vitro* experiments, is between 10^{-5} M and 10^{-8} M. In order to obtain a concentration of 10^{-8} M to 10^{-5} M in the human forearm it would have been necessary to supply 11 µg to 11 mg AVP/min/dl FAV. In the present study we used an AVP dose of 8 ng /min/dl because from previous experiments we knew the safety and efficacy of this dose in human experiments.[28] The computed plasma levels that were reached by this dose were between 0.7 and 6.0 ng/ml. With this dose we found a significant increase in endothelin production, albeit only after a preceding infusion of 30 mg L-NMMA. As we measured no significant rise after L-NMMA alone, nor after placebo infusion alone, it is reasonable to assume that AVP decisively contributed to the rise in endothelin production. The levels of AVP did not show a decline during the study but the levels stayed relatively stable. This observation suggests that AVP induces the endothelial release of nitric oxide which in turn inhibits the AVP-induced release of endothelin. Through blockade of NO synthesis, by L-NMMA, the AVP-induced release of endothelin is apparently unmasked. If higher concentrations of AVP had been used, L-NMMA might not have been necessary to demonstrate the AVP-induced increases in endothelin production. However, the use of high dosages of AVP in humans is restricted by the adverse effects of this substance. On the other hand the concentration of endothelin measured by means of the same radio-immunoassay kits in our study after AVP and L-NMMA infusion was of the same magnitude as that established in patients with advanced congestive heart failure, a condition

well known for leading to a considerable rise in endothelin levels.[29] Also from this respect higher doses of AVP might not be without adverse effects on the circulation. The rapid rise in endothelin concentrations that we detected *in vivo* underscores the results of previous studies that provided evidence for the release of endothelin via the regulated secretory pathway because such a relatively rapid rise is hardly in agreement with *de novo* synthesis but rather with release from endothelial storage granules.[25] There might also be factors that hamper the adequate detection of a rise in endothelin output such as a high local clearance of endothelin, by which it is possible that a high percentage of the locally raised endothelin production is metabolised before it reaches the plasma. Another contributing factor could be that about 75% of endothelin is possibly released via the albuminally.[25,30,31] As we measured a significant rise in endothelin levels in the plasma, the total rise in endothelin release must have been very high as the plasma levels we detected were as high as those in subjects with a chronic endothelin production stimulating condition such as congestive heart failure.[29] As the production or overflow as we defined it includes flow, flow could have an impact on the production if the flow changes had been large. But at the moments the highest endothelin productions were measured FBF was not always higher but sometimes even lower compared with the measurements at other time points. After the infusion of L-NMMA, the flow in the experimental arm in the groups in which this was done declined, but not significantly so. This seemingly contradictory effect is probably caused by the fact that no pulse cuff was adjusted to exclude the circulation of the hand. Because of this, no estimation of the effects of L-NMMA or AVP on FBF could be made. We deliberately did not use a pulse cuff as flow changes after L-NMMA or AVP were not the goal of this study. FBF was only measured to calculate endothelin production. Therefore, we also made no statistical comparisons between groups regarding flow data. Within groups the FBF can be considered relatively stable during the experiments and metabolic effects of flow changes can be regarded as of no importance to the outcome. We did not register a rise in endothelin production after four to five minutes, as has been found before.[8,9] But in those studies only endothelin concentration was measured so flow changes may have confounded the outcome. In our study the measurement of FBF was directly aimed at the correction for this factor.

In the present study the peak of endothelin production was observed after 15 minutes of AVP infusion that had been preceded by L-NMMA infusion for 15 minutes. This might indicate that the AVP effect on endothelin might dissolve quickly despite ongoing stimulation. There was an indication towards a higher output of endothelin during the entire period of AVP infusion in both groups compared

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with placebo, but these trends were not significant. So, whether this decline in the stimulatory effect is real or a result of the small groups we studied must be examined further.

Further experiments in this *in vivo* human model are warranted to unravel more about the endothelin physiology in the endothelium of the human forearm.

CONCLUSION

In healthy male subjects AVP induced a rise in endothelin production in the forearm within 15 minutes, but only after prior infusion of L-NMMA. This observation suggests that the AVP-induced production of nitric oxide offsets AVP-mediated release of endothelin.

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