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Venous responsiveness to atrial natriuretic factor in man

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The venorelaxant effect of atrial natriuretic factor in man was studied using the dorsal hand vein technique. Infusion of met-ANF to preconstricted veins at doses up to 240 ng min^{-1} in 11 healthy male subjects caused only minimal venorelaxation. Atrial natriuretic factor is unlikely to have a significant venorelaxant effect at physiological doses in man.

Keywords atrial natriuretic factor dorsal hand vein venous system

Introduction

Atrial natriuretic factors, known collectively as ANF, are found in mammalian heart and plasma. ANF decreases central blood volume by producing a natriuresis, inhibiting the release of aldosterone and inducing vascular relaxation, by activation of smooth muscle cyclic GMP accumulation (Richards *et al.*, 1985; Needleman & Greenwald, 1986). Systemic infusion of ANF in man causes hypotension and flushing, but whether the sites of vasodilatation are arterial, venous or both is unclear (Richards *et al.*, 1985). Studies on the vasorelaxant properties of ANF have been performed in *in vitro* animal systems using various arterial and venous preparations. Data from these studies have shown tissue and species differences, with variable venodilatory effect in different species (Winquist, 1985). In the rabbit, facial, pulmonary and renal veins relax with ANF whereas saphenous and iliac veins are insensitive (Faison *et al.*, 1985). How applicable these results are to man is unclear, and little is known about the specific vascular physiological and pharmacological actions of this hormone in man.

The purpose of this study was to quantify the venorelaxant properties of human met-ANF in healthy human subjects. The dorsal hand vein compliance technique was used because it permits complete dose-response studies of venous relaxation without confounding reflex alterations. If ANF were a potent vasodilator of the dorsal hand vein, this technique would provide a valuable *in vivo* model for studying mechanisms of ANF action.

Methods

Studies were conducted in 11 healthy male subjects, 18 to 75 years of age (mean ± s.d. 39.3 ± 20.2 years). All subjects were normotensive, were not taking any drugs, had normal electrolytes, complete blood count and ECG and were found to be in good general health. Subjects refrained from caffeine and alcohol intake for 12 h before the study.

The dorsal hand vein compliance technique, as modified by Aellig, was used as described in detail previously (Aellig, 1981; Pan *et al.*, 1986). Subjects were supine in a quiet room kept at a constant temperature of 72 ± 2°F. Recordings of the position of a linear variable differential transformer (LVDT) situated on the top of the vein were made both before and after inflation of a sphygmomanometer cuff on the same arm to 40 mm Hg. The difference between the two positions of the LVDT gave a measure of the diameter changes of the vein under the congestion pressure. All local drug infusions lasted for at least 5 min at a constant infusion volume rate of 0.37 ml min^{-1};

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the cuff was inflated for 2 min at intervals during each infusion period. Increasing concentrations of a drug were infused in a sequential manner.

Phenylephrine, an α-adrenoceptor selective agonist, was used to produce vasoconstriction of the hand vein. A dose-response curve to phenylephrine was performed in each subject (dose range: 20–5250 ng min^{-1}). In this way the doses of phenylephrine which produced 50% and 80% of the maximal venous constriction obtainable with phenylephrine were determined. The dose producing 80 ± 5% venous constriction was then infused at a constant rate ('preconstriction dose') during the infusion of increasing doses of human met-ANF (dose range 20–240 ng min^{-1}) which took 60 to 120 min. Previous experience has shown that phenylephrine-induced venoconstriction is stable during this time period. Venous relaxation was defined as a percentage of the baseline preconstriction by the formula (A-Y/X-Y) × 100 where A is vein diameter with ANF dose, X is baseline (prephenylephrine) vein diameter and Y is constricted (preANF) vein diameter. Following the met-ANF infusions, nitroglycerine was then infused, with the preconstriction dose of phenylephrine, at a dose of 70 ng min^{-1}, a dose we have previously found produces a maximal venous relaxation in most subjects (Eichler *et al.*, 1987).

Blood pressure and pulse were monitored on the opposite arm; in no case did the infused drugs cause a change in heart rate or blood pressure.

Results

There was wide interindividual variation in responsiveness to phenylephrine as has been previously found. The geometric mean of the dose of phenylephrine that produced 50% of maximal venoconstriction (ED_{50}) was 138 ng min^{-1}, (log mean ± s.d., 2.14 ± 0.37).

The venodilator effect of ANF was small compared with previous experience with other venodilators such as nitroglycerine and isoprenaline where the dorsal hand vein model has been found to be a sensitive technique for measuring venodilator effects (Eichler *et al.*, 1987; Pan *et al.* 1986). Results for each subject at the highest infused dose of ANF and with nitroglycerine are shown in Table 1. The mean venous relaxation at an infusion rate of 120 ng min^{-1} was 8% (range −12 to 32) and at 240 ng min^{-1} was 10% (range −12 to 32). In view of this small response, it was not possible to calculate the ED_{50} for ANF from the dose-response curve. The mean venous relaxation with nitroglycerine was 106% (range 81 to 152). The marked venodilation above 100% obtained in some subjects suggests that a degree of resting venoconstriction was present in these subjects.

Table 1 The results of the study

		Venous relaxation (% baseline)		
	Age	*ANF (ng min^{-1})*		*NTG*
Subject	*(years)*	*120*	*240*	*70 ng min^{-1}*
1	20	9	18	113
2	21	5	0	97
3	23	11	18	81
4	24	0	14	152
5	25	19	25	136
6	30	0	5	84
7	41	32	32	ND
8	44	−12	−12	ND
9	63	5	0	98
10	66	18	14	ND
11	75	4	0	89

ND – not determined

Discussion

The small venodilator effect of ANF on the dorsal hand vein was unexpected to us, as many blood vessels relax in response to this peptide (Thibault *et al.*, 1986). The rabbit study previously discussed and two more recent *in vivo* studies are, however, in agreement with our findings. In the rat, ANF, but not nitroprusside (which also acts by elevating cGMP), failed to alter noradrenaline-induced venoconstriction (Watkins *et al.*, 1987). A study of ANF induced relaxation in human saphenous vein segments showed no demonstrable effect, while intraarterial ANF infusion to human volunteers at a dose of 300 ng min^{-1} produced over a 100% increase in forearm blood flow, due to arterial dilatation (Hughes *et al.*, 1988). Although results in the dorsal hand vein model may not reflect venous responsiveness at other sites, our results suggest that ANF is unlikely to have significant venodilatory effect in man and that the hypotensive effect of ANF is due to arterial vasodilatation with subsequent reduction in afterload. The explanation for this arterial selectivity is not known. Differences in binding site density have not been found to correlate with vessel responsiveness (Thibault *et al.*, 1986). In conclusion, ANF has minimal venodilator action in human dorsal hand veins and this experimental model cannot be used to further elucidate the mechanisms of action and physiological significance of ANF in man.

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Since acceptance of this paper, Webb *et al.* (1988), *Br. J. clin. Pharmac.*, **26**, 245–251, have also shown that ANF lacks venodilatory activity in man.