Role of endogenous opioids and catecholamines in vasovagal syncope

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Head-up tilt testing demonstrates vasovagal mechanisms as a cause for syncope, but the pathophysiology underlying this condition remains unclear. The aim of this study was (i) to measure plasma β-endorphins, adrenocorticotropic hormone, cortisol, catecholamines, and brain natriuretic peptide during head-up tilt, and (ii) to assess the effect of naloxone infusion during head-up tilt in subjects with reproducible vasovagal syncope. During the assessment of unexplained syncope, 71 subjects underwent a total of 93 tilt tests (60-70° head upwards for 40-45 min or until syncope occurred) during which frequent blood sampling was performed. Subjects with a positive tilt test (n = 56) (mean duration to syncope 23.6 min) showed a larger rise in β-endorphin levels prior to syncope (baseline 4.7 ± 2.2 vs syncope onset 6.9 ± 3.2 pmol. l⁻¹, P=0.0001) than those with a negative test (n=37) (baseline 3.9 ± 3.9 vs end of test 4.9 ± 2.3 pmol. l⁻¹, P=0.03). During tilting, adrenocorticotropic hormone, cortisol, and noradrenaline increased; adrenaline and brain natriuretic peptide remained unchanged; and these responses were similar in positive and negative test groups. Naloxone (2.6 mg. kg⁻¹ i.v. bolus followed by 20 μg. kg⁻¹.min⁻¹ infusion), administered in a double-blind fashion during head-up tilt in nine subjects, failed to modify either the time to syncope or the vasodepressor response. Thus, endogenous opioids appear not to be an important trigger for vasovagal syncope, and other pathophysiological mechanisms should be considered.

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Key Words: Vasovagal syncope, tilt-testing, opioids, β-endorphin, naloxone, catecholamines.

Introduction

Patients with syncope constitute between 1–3% of attendances at the emergency department and 3–6% of medical admissions[1]. In 30–50% of cases no underlying cause is found despite extensive investigation[2]. Whilst the introduction of head-up tilt testing has facilitated the diagnosis of vasovagal (vasodepressor) syncope[3], understanding of the pathophysiology of this condition remains poor. The mechanism of syncope may be similar to the Bezold-Jarisch reflex[4]. It has been considered that afferent signals in non-myelinated vagal C-fibres cause reflex reduction in sympathetic tone[5] and increased vagal activity, but the fact that vasovagal reactions can occur after cardiac transplantation, in the absence of demonstrable vagal reinnervation, suggests a role for alternative non-cardiac triggers[6]. These potential triggers include psychological factors, vasopressin release, carotid sinus baroreceptors, and pulmonary mechanoreceptors[7].

The high concentrations of opioid containing nerve cells and receptors found in the brainstem 'cardiovascular centres' has generated interest in the possible physiological regulation of baroreceptor mechanisms by endogenous opioids. In animal studies, using a rabbit model of haemorrhagic shock, administration of an opioid agonist (methionine–enkephalin) produced hypotension and bradycardia (akin to a vasovagal reaction)[8]. Naloxone, administered either intravenously or intracisternally, prevented the vasodepressor response induced by progressive haemorrhage[9]. Sneddon et al. demonstrated that patients with tilt-induced syncope had significantly enhanced cardiopulmonary baroreceptor mediated vasoconstriction in response to lower body negative pressure[10]. The observation that naloxone can enhance baroreflex sensitivity in normal subjects suggests that endogenous opioids have a tonic inhibitory effect on baroreflex mechanisms[11,12]. Plasma β-endorphins have been demonstrated to rise in patients following vasodepressor syncope, but it is unclear whether this represents a primary or secondary phenomenon[13]. In a preliminary report of 24 patients,
prior to vasovagal syncope, but the pathophysiological significance of this observation remains uncertain\(^\text{[14]}\).

To elucidate the triggering mechanisms in vasovagal syncope, we wished to determine whether the preliminary observation of a rise in plasma \(\beta\)-endorphins was reproducible in a larger population. In support of a putative role for endogenous opioids, it was considered important to examine whether infusion of naloxone could modify the vasovagal response. The role of other factors, such as catecholamines and brain natriuretic peptide (BNP), was also examined.

### Methods

#### Subjects

Ninety-three consecutive tilt tests were performed in 71 subjects for the assessment of unexplained syncope. The clinical characteristics of the subjects are shown in Table 1. Regular medication was continued prior to the test.

### Tilt test

All tests were performed in the fasting state between 0930 and 1230h. Patients were tilted 60° upwards for 40–45 min: an angle of at least 60° having been previously shown to be required for adequate test sensitivity\(^\text{[13]}\). Both continuous (Finapres: Ohmeda, Hatfield, U.K.) and intermittent (Dinamap: Critikon, Bracknell, U.K.) non-invasive measurement of blood pressure was performed. An antecubital venous cannula, inserted 15 min prior to the test, permitted frequent blood sampling for \(\beta\)-endorphin, adrenocorticotrophic hormone, cortisol, brain natriuretic peptide (BNP), and catecholamines. Aliquots of 20 ml were obtained at baseline, and then every 10 min, or at the onset of symptoms or syncope (a maximum of 120 ml per test).

### Naloxone protocol

Thirteen subjects with frequent spontaneous syncope and a vasovagal response demonstrated by previous tilt testing were considered for the naloxone study. The study design required tilt testing (60° for up to 45 min) on three separate occasions: a ‘diagnostic’ baseline test (by definition positive); and then in a double-blinded fashion, tests with either infusion of placebo or naloxone. Four subjects were excluded due to a negative baseline test, and nine subjects completed the naloxone protocol. Naloxone (Sigma Chemicals, Poole, U.K.) was administered as a loading dose (2.6 mg kg\(^{-1}\) i.v.) over the 15 min prior to tilt, followed by a maintenance infusion (20 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) continued throughout the test. The dose of naloxone was derived from our previous experience of blood levels obtained during naloxone infusion in patients with ischaemic heart disease\(^\text{[16]}\).

### Analytical

#### Beta endorphin

Beta endorphin was measured by liquid phase radioimmunoassay following extraction from plasma using C18 Sep-Pak cartridges. The primary antiserum cross-reacted by 2% with human \(\beta\)-lipotrophin (Peninsula Laboratories Inc., Belmont, CA, U.S.A.) and by <0.01% with other related peptides. The sensitivity of the assay was 3 pmol l\(^{-1}\). The within-batch coefficient of variation over the concentration range 12 to 60 pmol l\(^{-1}\) was 5%, and 10% at 7 pmol l\(^{-1}\). The between-batch variation for corresponding ranges was 8% and 12%, respectively. The normal range (mean ± 2 SD) of this assay in 60 volunteers sampled at 0900 h was 2.5–7.2 pmol l\(^{-1}\).

#### Adrenocorticotrophic hormone

Adrenocorticotrophic hormone was quantified in unextracted plasma by radioimmunoassay employing \(^1\text{25}\) human adrenocorticotrophic hormone (1–39) tracer and an N-terminal antibody\(^\text{[17]}\). The assay was standardized against the WHO reference preparation of human corticotrophin (NIBSC reagent 74/555). The sensitivity of the method was 3 mU l\(^{-1}\). The within-batch coefficient of variation was <10% between 6–200 mU l\(^{-1}\). Between-batch variation was 15% at mean concentrations of 20, 80 and 200 mU l\(^{-1}\). Adrenocorticotrophic hormone levels taken from normal individuals between 0700 and 0900 h are usually <20 mU l\(^{-1}\).

#### Cortisol

Cortisol was measured using a direct solid phase radioimmunoassay\(^\text{[18]}\). The within-batch coefficient of variation was 6% between the concentration range 30–600 nmol l\(^{-1}\) and the between-batch variation was 10% at the mean levels of 75, 400 and 760 nmol l\(^{-1}\). Normal ranges were 280–720 nmol l\(^{-1}\) between 0700 and 0900 h and 60–340 nmol l\(^{-1}\) between 2100 and 2400 h.

#### Plasma catecholamines

Plasma catecholamines were estimated by HPLC using electrochemical detection. Noradrenaline levels are usually <5 nmol l\(^{-1}\) and those of adrenaline <0.4 nmol l\(^{-1}\).

Brain natriuretic peptide was extracted from acidified plasma using C8 columns. Concentrate eluants were then assayed using a commercially available radioimmunoassay (Peninsula Laboratories Inc., Belmont, CA, U.S.A.). The antiserum does not cross-react with human atrial natriuretic peptide (ANP) or other related hormones.

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### Table 1: Clinical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Negative tilt test</th>
<th>Positive tilt test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/M/F</td>
<td>37/22</td>
<td>56/36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.9 ± 16.0</td>
<td>47.7 ± 16.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Beta-blocker/disopyramide</td>
<td>4/1</td>
<td>3/2</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

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\(1\) We showed that plasma \(\beta\)-endorphin levels increase prior to vasovagal syncope, but the pathophysiological significance of this observation remains uncertain\(^\text{[14]}\).

\(2\) Methods

\(3\) Subjects

\(4\) Tilt test

\(5\) Naloxone protocol

\(6\) Analytical

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Eur Heart J, Vol. 17, November 1996
Table 2 Plasma β-endorphin (PBE) and haemodynamic responses to upright tilt

<table>
<thead>
<tr>
<th>Duration (min)</th>
<th>PBE (pmol.l⁻¹)</th>
<th>Heart rate (beats.min⁻¹)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (n=37)</td>
<td>Baseline</td>
<td>3.9 ± 1.6</td>
<td>69.0 ± 11.9</td>
<td>141.3 ± 21.4</td>
</tr>
<tr>
<td></td>
<td>End of test</td>
<td>4.9 ± 2.3*</td>
<td>76.6 ± 12.1</td>
<td>141.5 ± 25.4</td>
</tr>
<tr>
<td>Positive (n=56)</td>
<td>Baseline</td>
<td>4.7 ± 2.2</td>
<td>73.9 ± 11.9</td>
<td>133.6 ± 18.5</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>6.9 ± 3.2**</td>
<td>61.7 ± 21.4*</td>
<td>81.1 ± 22.2†</td>
</tr>
</tbody>
</table>

*P<0.03 vs baseline.
**P<0.001 vs baseline and P=0.004 vs negative end of test.
***P<0.002 vs baseline and P=0.0002 vs negative end of test.
†P<0.0001 vs baseline and P=0.0001 vs negative end of test.

peptides. The sensitivity was 7 pmol.l⁻¹. Previously reported normal values for a similar extraction method and the same kit are 4.9 ± 1.7 pmol.l⁻¹.

Naloxone was extracted from serum by solid phase techniques and quantified by high performance liquid chromatography with electrochemical detection (modified from 20). The lower limit of detection was 10 nmol.l⁻¹ with a mean recovery of 95% from 1 ml samples of serum spiked with 500 pmol naloxone measured by a HPLC method. The following drugs were shown not to interfere: dihydrocodeine to 4.5 pmol.l⁻¹, salicylate to 1.5 mmol.l⁻¹, paracetamol to 1.0 mmol.l⁻¹, propranolol, metoprolol, diltiazem, nifedipine and captopril. Precision was 5.0% at 200 nmol.l⁻¹ and 4.8% at 900 nmol.l⁻¹.

Statistics

Following assessment of normality of distribution, data were compared by either a t-test or Mann–Whitney test as appropriate. Multiple group comparisons were performed by analysis of variance. Results are shown as mean values (± SD) and differences were considered significant at P<0.05.

Ethical approval

The administration of naloxone during tilt testing was approved by the Ethical Committee of Glasgow Royal Infirmary, and subjects gave written informed consent. Verbal consent was obtained for blood sampling.

Results

Response to tilt testing

A vasovagal response was induced during 56 of 93 tilt tests, and the mean time to syncope was 23.6 ± 10.9 min (Table 2). Mean age, clinical characteristics (Table 1) and baseline haemodynamics (Table 2) were similar in positive and negative test groups. The vasovagal response was typically characterized by hypotension (vasodepressor syncope). Asystole of abrupt onset was observed in only four tests. The maximal heart rate during tilt in the negative test group (86.4 ± 17.3 beats.min⁻¹) was similar to the heart rate immediately prior to vasovagal syncope in the positive test group (87.4 ± 24.6 beats.min⁻¹).

Plasma beta endorphin levels

Subjects with a negative test showed a small rise in plasma β-endorphins (P=0.03) in response to head-up tilt (Table 2 and Fig. 1). By comparison, a positive test response was associated with a more pronounced increase in plasma β-endorphins (P<0.0001) to a level prior to vasovagal syncope that was significantly greater than that at the end of a negative test (P=0.004). Included in these results are β-endorphin responses in 12 subjects with a positive test who underwent repeat testing: concordant responses were observed in 11 subjects with a second positive test, whilst two subjects with a negative repeat test showed little change in β-endorphin (concordant in one subject; a new feature relating to successful treatment with disopyramide in one subject).

Naloxone infusion

The mean age of the nine subjects completing the naloxone study was 42.8 ± 16.8 years. Infusion of naloxone was well tolerated (Table 3) and mean blood naloxone levels achieved during the maintenance infusion were 3421 ± 1123 nmol.l⁻¹. Vasovagal syncope was induced in 26 of 27 tilt tests performed as part of this study (one subject had a negative test during placebo infusion). Naloxone failed to significantly modify either the time to syncope (Table 3 and Fig. 2) or the hypotensive response (Table 3). Plasma β-endorphin levels increased during infusion of naloxone, but the levels immediately prior to syncope were not significantly different in any of the three tests.

Catecholamines

Plasma catecholamine levels at baseline and in response to tilt were similar in the positive and negative test...
Figure 1  The plasma β endorphin (PBE) response to tilt testing. Subjects with induced vasovagal syncope (positive) show an augmented rise in PBE ($P=0.0001$) compared to those with a negative result ($n=37$) ($P=0.03$). ULN = upper limit of normal.

Figure 2  Time to syncope during tilt testing at baseline and during double blind infusion of either placebo or naloxone ($n=9$).

Figure 3  The plasma noradrenaline response to tilt testing. In all subjects ($n=8$) tilt is associated with an immediate increase in noradrenaline (baseline: 2.37 ± 0.65 vs 5 min: 4.07 ± 0.75; $P=0.003$). ○ = negative test; ▲ = positive test.

Cortisol and adrenocorticotropic hormone

Changes in plasma adrenocorticotropic hormone were similar in magnitude and direction to β-endorphin, with an augmented rise in subjects with a vasovagal response to head-up tilt (Table 4). Plasma cortisol level changed in parallel with plasma adrenocorticotropic hormone.
Table 3 Effects of naloxone (or placebo) infusion during tilt testing in subjects (n=9) with easily reproducible vasodepressor syncope. Observations for the period 'infusion' were made after the loading dose of naloxone, and immediately prior to the commencement of a maintenance infusion and upright tilt

<table>
<thead>
<tr>
<th></th>
<th>Duration (min)</th>
<th>PBE (pmol. l⁻¹)</th>
<th>Heart rate (beats min⁻¹)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23±4 ± 150</td>
<td>54 ± 3.2</td>
<td>749 ± 12.9</td>
<td>129 ± 15.5</td>
<td>776 ± 8.0</td>
</tr>
<tr>
<td>Syncope</td>
<td>20±3 ± 12.5</td>
<td>83 ± 3.4</td>
<td>755 ± 18.5</td>
<td>780 ± 8.9</td>
<td>479 ± 10.2</td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>—</td>
<td>12 ± 2.2</td>
<td>723 ± 12.4</td>
<td>127 ± 18.7</td>
<td>773 ± 7.3</td>
</tr>
<tr>
<td>Infusion</td>
<td>—</td>
<td>51 ± 3.5</td>
<td>728 ± 13.3</td>
<td>132 ± 15.3</td>
<td>792 ± 8.2</td>
</tr>
<tr>
<td>Syncope</td>
<td>10±8 ± 11.6</td>
<td>51 ± 2.6</td>
<td>776 ± 15.2</td>
<td>71 ± 10.5</td>
<td>468 ± 7.1</td>
</tr>
<tr>
<td>Naloxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>—</td>
<td>44 ± 2.3</td>
<td>721 ± 11.9</td>
<td>124 ± 18.4</td>
<td>762 ± 7.7</td>
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<tr>
<td>Infusion</td>
<td>—</td>
<td>86 ± 6.0</td>
<td>730 ± 11.1</td>
<td>125 ± 15.6</td>
<td>748 ± 7.3</td>
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<tr>
<td>Syncope</td>
<td>10±8 ± 11.6</td>
<td>51 ± 2.6</td>
<td>776 ± 15.2</td>
<td>71 ± 10.5</td>
<td>468 ± 7.1</td>
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</tbody>
</table>

Table 4 Endocrine response to tilt testing

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Baseline</td>
</tr>
<tr>
<td>Adrenaline (nmol. l⁻¹)</td>
<td>9</td>
<td>0.15 ± 0.05</td>
</tr>
<tr>
<td>Noradrenaline (nmol. l⁻¹)</td>
<td>9</td>
<td>1.95 ± 1.18</td>
</tr>
<tr>
<td>ACTH (mU. l⁻¹)</td>
<td>17</td>
<td>4.3 ± 2.2</td>
</tr>
<tr>
<td>Cortisol (nmol. l⁻¹)</td>
<td>25</td>
<td>333 ± 202</td>
</tr>
<tr>
<td>BNP (pmol. l⁻¹)</td>
<td>2</td>
<td>4.8 ± 1.8</td>
</tr>
</tbody>
</table>

*P<0.02 vs baseline.
**P<0.005 vs baseline.
***P<0.0001 vs baseline.
†P<0.0005 vs baseline.

Brain natriuretic peptide

Plasma levels of BNP were unchanged in response to head-up tilt (Table 4).

Discussion

A traditional view of vasovagal syncope

The classical features of the fainting reaction were described by Cotton and Lewis in 1918 and the term vasovagal syncope was first used by Lewis in 1932. The initial physiological adaptation to the fall in venous return that accompanies orthostasis is a baroreceptor-mediated rise in sympathetic tone, with maintenance of blood pressure at near normal levels by an increase in heart rate and vascular tone. Vasovagal syncope is characterized by the dramatic interruption of this compensatory response, with a simultaneous decrease in blood pressure and heart rate, mediated by a reduction in sympathetic tone and an increase in vagal tone. The nuclei in the medulla that trigger parasympathetic activity (the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve) and sympathetic activity (the rostral ventromedial and ventrolateral medulla) are modulated by sensory input from arterial baroreceptors and cardiac mechanoreceptors. The prevailing hypothesis is that in the face of central hypovolaemia, due either to gravitational effects or to haemorrhage, ventricular diastolic filling may become critically compromised. The positive inotropic effect of circulating catecholamines deforms the relatively empty ventricle, activating cardiac mechanoreceptors. Afferent signals, conveyed in non-myelinated vagal C-fibres to the medullary nuclei, cause the reflex reduction in sympathetic tone and increased vagal activity.

Why other potential mechanisms must be implicated

The report by Fitzpatrick et al. of vasovagal reactions during passive upright tilt in heart transplant recipients without evidence of cardiac reinnervation has led to a reappraisal of the ventricular baroreceptor hypothesis and a search for alternative explanations. In previous experimental studies it had been observed that bilateral vagotomy failed to prevent the paradoxical fall in renal sympathetic nerve activity (akin to a vasovagal reaction) seen during haemorrhage in conscious dogs. Also, despite the addition of profound stimulation by aortic occlusion, only 20% of ventricular afferent fibres
increased their firing during haemorrhage or caval occlusion.[26]

**Endogenous opioids and baroreflexes**

There is widespread distribution of opioid peptides and receptors both centrally and peripherally within the autonomic nervous system, at sites suggesting close functional involvement with cardiovascular regulation.[27] It has been proposed that endogenous opioid mechanisms have an important influence on the haemodynamic responses to acute blood loss.[28] Opiate receptors are involved in the paradoxical decrease in sympathetic renal activity seen during hypotensive haemorrhage in conscious rabbits, due to activation of cardiac receptors or to low-pressure baroreceptors in the thoracic vessels or pulmonary circulation.[29,30] Naloxone, administered either intravenously[31] or intracisternally,[32] has been shown to prevent, or reverse, the vasodepressor response in a rabbit model of haemorrhagic shock. Beta-endorphin is released from the pituitary in equimolar concentrations with adrenocorticotrophic hormone[33], and it has been shown that hypophysectomy abolishes the post haemorrhage pressor action of naloxone.[34]

In human studies, using incremental lower body negative pressure, naloxone enhanced the cardiopulmonary baroreflex excitation of muscle sympathetic nerve activity.[35] Similarly, whilst naloxone markedly attenuated hypotension induced by sodium nitroprusside, a long acting enkephalin analogue (DAMME) exaggerated the effect.[36] These data, suggesting that endogenous opioids exert a tonic inhibitory effect on cardiopulmonary baroreflexes, must be contrasted with the observation that patients with tilt-induced syncope have significantly greater cardiopulmonary baroreceptor-mediated vasoconstriction in response to minor degrees of hypovolaemia induced by lower body negative pressure than a control group with unexplained syncope but a negative tilt test response.[37] Unfortunately this study did not determine whether this enhanced susceptibility was due to a greater decrease in venous return or to primary augmented cardiopulmonary baroreceptor sensitivity.

**The present results**

We have demonstrated an increase in plasma beta-endorphin levels prior to the onset of symptoms or syncope in subjects with vasovagal syncope induced by tilt testing. A variety of beta-endorphin responses were observed (Fig. 1), with an increase above the normal range in 35% of subjects in the positive test group, compared to 18% in the negative test group. Given this, and the experimental evidence that endogenous opioids play an important role in the triggering of vasodepressor events, it is necessary to explain the failure of naloxone to modify the vasovagal response in the present study.

The subjects included in the naloxone study were well characterized, with frequent spontaneous syncope and a reproducible vasovagal response to tilt testing (there was just one negative test during the study). Subjects were not selected on the basis of a known increase in plasma beta-endorphins in response to tilt, and plasma beta-endorphin levels at baseline and prior to syncope were similar to the larger consecutive series (Tables 2 and 3). Naloxone administration caused no symptomatic or haemodynamic upset that could have interfered with the double-blinding process. The dose of naloxone was based on our previous experience of administration of this drug in human heart failure.[38] An in vitro concentration of 1–100 nmol L⁻¹ causes antagonism at all opioid receptor subtypes.[39,40] Adequate plasma concentrations were, therefore, obtained in the present study.

**Plasma catecholamines**

The plasma catecholamine response during vasovagal syncope has been examined by several authors. Goldstein et al.[35] reported one subject who showed no increase in plasma noradrenaline during hypotension induced by venepuncture, despite normal noradrenaline responses to orthostasis, exercise and sodium nitroprusside infusion. Interestingly, an intravenous bolus injection of 50 mg naloxone in this subject had no beneficial effect on blood pressure. Plasma noradrenaline levels show an initial rise with head-up tilt and an abrupt fall with syncope, reflecting a withdrawal of sympathetic tone.[38,39] Adrenaline levels rise immediately after syncope suggesting increased adrenal output. This discrepancy in the behaviour of catecholamines occurs characteristically during, and following, the vasovagal event. The present study confirms that the catecholamine response to tilt is similar in the positive and negative test groups. The fact that catecholamines do not change immediately prior to syncope suggests that other trigger mechanisms must be involved.

**Are other endocrine mechanisms important?**

The concentrations of immunoreactive adrenocorticotrophic hormone in peripheral circulating blood parallel those of beta-endorphin, since these polypeptides are derived from the same precursor protein (proopiomelanocortin); are stored together in secretory granules of the pituitary corticotrophs; and are released together in response to corticotrophin-releasing factor and arginine vasopressin[40]. Baroreceptors located in the right atrium are the dominant mediators of adrenocorticotrophic hormone secretion in response to haemodynamic stimuli.

The secretion of vasopressin is influenced primarily by plasma osmolality, and secondarily by changes in blood pressure and by nausea. Pharmacological blockade of cardiac nerves during progressive
haemorrhage in conscious dogs prevents a fall in blood pressure and attenuates the increase in vasopressin but the situation is more complex in humans, with a normal vasopressin response to blood volume shifts in transplant patients. The reports of a rise in plasma arginine vasopressin before vasovagal syncope raise the possibility that neuroendocrine changes play a major part in 'sensitizing' left ventricular baroreceptors to circulating catecholamines. In a canine model it has been shown that the systemic and coronary vasoconstriction which follows the intracerebral administration of the opiate agonist fentanyl is mediated via the release of arginine vasopressin. We have previously demonstrated a correlation between β-endorphin and arginine vasopressin concentrations in patients with myocardial ischaemia.

Brain natriuretic peptide (BNP) has similar biological effects to ANP, but is predominantly synthesised in the ventricle and release may involve a stretch-release coupling mechanism. It has been hypothesised that ANP exerts its cardiovascular effects by interacting with autonomic control mechanisms. The observation that blockade of afferent vagal C-fibres abolished the inhibition of renal sympathetic nerve activity produced by ANP raises the possibility that ANP might have a paracrine function to stimulate chemo-sensitive cardiac vagal afferents.

A variety of other putative triggers have been investigated. Adenosine triphosphate infusion can provoke vasodepressor syncope in susceptible individuals, and treatment with low-dose theophylline may prevent tilt-induced and spontaneous vasovagal syncope. Central intracerebroventricular serotonin induces hypotension, inhibition of renal sympathetic activity, and excitation of adrenal sympathetic activity. Vasovagal syncope may be prevented by the selective serotonin reuptake inhibitor fluoxetine hydrochloride. Pancreatic polypeptide increases during and following vasovagal syncope, presumed to be due to prolonged activation of central vagal centres.

In conclusion, an increase in plasma β-endorphins precedes syncope in many subjects with a vasovagal response to tilt testing. The increase in plasma β-endorphin levels may relate to co-release with adrenocorticotrophic hormone from the pituitary in response to simulation of low-pressure atrial baroreceptors by relative central hypovolaemia. The failure of adequate doses of naloxone to modify the vasovagal response suggests that endogenous opioid mechanisms are not an important trigger for vasovagal events in humans.

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References


