Release of Vasopressin, Cortisol and β -Endorphin in Tetraplegic Subjects in Response to Head-up Tilt

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Summary

Plasma levels of β -endorphin, vasopressin and cortisol during head-up tilt were measured in tetraplegic patients and in normal healthy subjects. In tetraplegic patients rapid tilt from the horizontal to 30° or 60° head-up induced orthostatic hypotension and increased plasma levels of cortisol, β -endorphin and vasopressin. In control subjects head-up tilt failed to alter plasma levels of these hormones. These data show that the head-up position in tetraplegics causes various endocrine reactions.

The normal mechanism by which blood pressure is maintained on the assumption of an upright posture (the orthostatic reflex) is absent in tetraplegic patients. In normal individuals, the orthostatic reflex comprises an afferent system involving baroreceptor input through the ninth and tenth cranial nerves and an efferent effector system that is primarily the peripheral sympathetic system. This orthostatic reflex arc is broken by spinal cord transection, so that tetraplegic subjects show marked hypotension in response to the upright posture. In these subjects this orthostatic hypotension stimulates emergency endocrine reactions (Stephen, 1984). Tilting and standing of the tetraplegic subjects usually results in increased levels of vasopressin (Sved *et al.*, 1985), cortisol (Vallbano *et al.*, 1966), aldosterone and plasma renin activity (Johnson and Park, 1973; Mathias *et al.*, 1975, 1980; Kamelhar *et al.*, 1978; Kooner *et al.*, 1988).

In the present study we have demonstrated that the increases in plasma levels of cortisol and vasopressin are associated with increase in levels of plasma β -endorphin during the head-up position of tetraplegic subjects.

Methods

Subjects

We studied 8 tetraplegic patients (4 men and 4 women) with spinal cord transection and 5 healthy volunteers, all having given informed consent. The ages of the

patients ranged from 13 to 63 years. The normal volunteers were three healthy males and 2 healthy females, aged 29 to 34 years.

Experimental protocol

Subjects were placed on a tilt table and firmly belted in position with four straps at ankles, knees, hips, and chest. A 20-gauge scalp vein heparin lock was inserted in an antecubital vein. After each subject rested in the horizontal position for at least 15 minutes, blood pressure and heart rate were recorded, and then a blood sample was collected. Blood pressure and heart rate were measured with an automatic sphygmomanometer (Copal Model UA-231, Electronic Digital Blood Pressure and Pulse Meter, PETAŞ LTD, İstanbul, Turkey). Two minutes later, the subject was tilted from horizontal to 30° head-up in 2 minutes and retained in the head-up position for 15 minutes. At the end of 15 minutes the blood pressure and heart rate were recorded and blood samples were obtained. The subjects were returned to the horizontal and allowed to rest. Some normal healthy volunteers and 7 of 8 tetraplegic subjects were subjected to the 60° head-up tilt procedure session within 3 to 20 days from their first (30° head-up tilt) session.

Blood samples (6–8 ml) were obtained through an indwelling 20-gauge needle inserted into an antecubital vein prior to the study and kept patent by irrigation with a heparinised saline solution. Blood samples were obtained just prior to tilt and after 15 minutes of tilt. After collection of each sample, the venous line was flushed with 5 ml of saline. Samples were obtained using a plastic syringe, and were transferred immediately to plastic tubes containing 50 mg EDTA and placed on ice. Blood samples were centrifuged at 4°C (1500 g for 15 minutes), and the aliquots of plasma removed and frozen (–20°C) until assayed for vasopressin, β -endorphin and cortisol.

Plasma β -Endorphin, Vasopressin and Cortisol assay

β -Endorphin and Vasopressin were measured in 1 ml aliquots of plasma by radioimmunoassay after extraction of the peptides by SEP-PAK cartridges using commercially available radioimmunoassay kits (β -Endorphin RIA kit, NEK-003, New England Nuclear, Boston, MA, USA and Vasopressin RIA kit, Bülmann Laboratories AG, Basel, Switzerland). The recovery of vasopressin and β -Endorphin from the plasma were about $65 \pm 3\%$ and $74 \pm 4\%$ respectively. Cortisol was measured in 0.1 ml aliquots of plasma using commercially available radioimmunoassay kit (Kallestad Diognastic, TX, USA). All samples were run in the same assay; the intra-assay coefficients of variation, as determined by 5 replicate aliquots of pooled plasma obtained from control subjects during the horizontal position, were $8 \pm 2\%$, $7 \pm 2\%$ and $4 \pm 1\%$ for β -endorphin, vasopressin and cortisol respectively.

Statistics

Results are given as mean values $\pm$ SEM. Student's t-test for paired samples was used to assess significance level between pre-tilt values and post-tilt values. Significant difference from corresponding value for control subjects, as determined

by analysis of variance and the Tukey's procedure. Two-tailed P value less than 0.05 was considered significant.

Results

Baseline (pre-tilt) blood pressure (systolic/diastolic) and heart rate were $115 \pm 6/73 \pm 5$ mmHg and 79 ± 3 beats/minute or $122 \pm 17/75 \pm 10$ mmHg and 69 ± 3 beats/minute in tetraplegics or in controls respectively. In response to the 30° head-up position all 8 tetraplegics demonstrated marked hypotension (averaged decrease was 29 ± 6 mmHg, $p < 0.01$, or 18 ± 4 mmHg, $p < 0.05$, in systolic and diastolic blood pressure respectively) and tachycardia (the mean increase in heart rate was 19 ± 4 beats/minute; $p < 0.01$). Blood pressure and heart rate did not change after 30° head-up tilt in normal subjects. Two of 7 tetraplegics fainted within 3 to 5 minutes following 60° tilting and they were not included in the results. The arterial blood pressure fell following 60° tilting in 5 tetraplegic patients from a pre-tilt value of $111 \pm 7/68 \pm 3$ mmHg to $78 \pm 7/50 \pm 6$ mmHg ($p < 0.01$). In these patients the heart rate rose during head-up tilt from a pre-tilt value of 78 ± 4 beats/minute to 105 ± 3 beats/minute ($p < 0.01$). In control subjects baseline value of systolic pressure, 113 ± 4 mmHg, remained essentially unaltered, but diastolic pressure and heart rate tended to increase from pre-tilt value of 67 ± 3 mmHg to 78 ± 4 mmHg and 69 ± 2 beats/minute to 80 ± 5 beats/minute following 60° tilting from horizontal position.

Baseline plasma levels of β -endorphin, vasopressin and cortisol were not

Table Plasma levels of β -Endorphin, Vasopressin and Cortisol during the head-up position in tetraplegic and in normal subjects

Hormones position	Control	Tetraplegic
β -Endorphin (pg/ml)		
Horizontal	13.5 ± 3.6 (4)	15.4 ± 1.8 (8)
Head-up (30°)	13.3 ± 2.2 (4)	22.8 ± 3.1 (8) *
Horizontal	13.6 ± 2.1 (4)	11.6 ± 1.3 (5)
Head-up (60°)	18.0 ± 5.6 (4)	30.4 ± 1.6 (5) **
Vasopressin (pg/ml)		
Horizontal	3.8 ± 0.3 (5)	4.1 ± 0.2 (8)
Head-up (30°)	3.3 ± 0.9 (5)	6.6 ± 1.4 (8)
Horizontal	4.0 ± 1.0 (5)	4.8 ± 0.9 (5)
Head-up (60°)	5.2 ± 1.2 (5)	8.7 ± 0.5 (5) **
Cortisol (ng/ml)		
Horizontal	97 ± 18 (5)	115 ± 5 (7)
Head-up (30°)	85 ± 4 (5)	151 ± 6 (7) *
Horizontal	97 ± 17 (5)	123 ± 6 (5)
Head-up (60°)	132 ± 15 (5)	184 ± 16 (5) **

Data were given as mean $\pm$ SEM. Numbers in parenthesis indicate number of measurements. Significantly higher (* $p < 0.05$; ** $p < 0.01$) when compared with the value obtained at horizontal position

significantly different in patients and controls (Table). β -Endorphin, vasopressin and cortisol levels in plasma markedly increased in the tetraplegics, during the head-up position at the 60° . The increases in plasma β -endorphin and cortisol levels were also significant (Table) at the 30° in the patients. The increase in plasma

levels of vasopressin failed to reach significant level at the 30°. The levels of β -endorphin, vasopressin and cortisol in plasma remained unaltered during the 30° or 60° head-up position of the normal control subjects (Table).

Discussion

These results show that plasma levels of β -endorphin, vasopressin and cortisol increase in tetraplegic patients is a response to head-up position. Since these endocrine reactions were absent in normal healthy volunteers, the reactions apparently resulted from orthostatic hypotension in tetraplegic subjects.

The increased release of vasopressin in tetraplegic subjects in response to a head-up tilt was first suggested several years ago by Vallbona *et al.* (1966), and recently demonstrated by Sved *et al.* (1985). Our present results are consistent with these previous reports and show that the levels of vasopressin in plasma increased about twofold in tetraplegic subjects during the head-up position at 60° (Table). Vasopressin is a powerful pressor substance and is probably important in the maintenance or elevation of blood pressure in certain circumstances (Reid and Schwartz, 1984). Taken together, with the evidence that vasopressin released in response to head-up tilt in these subjects (Table; Sved *et al.*, 1985) suggest that vasopressin is involved in the maintenance of blood pressure in the head-up position in tetraplegic patients.

To date there has been no reported study of the β -endorphin responses in tetraplegic patients. Our observation that basal plasma levels of β -endorphin were normal in tetraplegic subjects agrees with a recent report (Polinsky *et al.*, 1987) which showed that peripheral catecholaminergic activity is not essential for basal or stress-induced release of β -endorphin from the pituitary in humans. The results of this study also indicate that head-up tilt elicits an increase in plasma β -endorphin levels in tetraplegic patients but not in normal subjects (Table). Plasma levels of β -endorphin are elevated due to its increased release from the pituitary in response to a variety of stressfully and emergency situations (Akil *et al.*, 1984; Martin, 1984; Polinsky *et al.*, 1987). In response to a head-up tilt all of the tetraplegics demonstrated marked hypotension (see results). Thus, it is likely that the observed increase in plasma levels of β -endorphin (Table) in the tetraplegics during a head-up tilt may result from the 'stress' effect of orthostatic hypotension. In addition to the stress effect, whether β -endorphin response to hypotension is also mediated by specific local baroreceptors and/or by intrathoracic receptors, is presently not known. Release of β -endorphin from the pituitary is usually, but not always, associated with the increased release of ACTH (Akil *et al.*, 1984). In the present study we did not directly measure plasma levels of ACTH, but the observed increases in plasma levels of cortisol strongly suggest that plasma levels of ACTH may also be elevated during the head-up position in tetraplegic patients.

The fall in blood pressure during a head-up tilt of tetraplegics can be due to impaired metabolism and clearance of the hormones measured, because of reduced hepatic and renal perfusion. Thus, it is likely that the observed increases in plasma levels of the hormones measured may result from, in part, their impaired metabolism, rather than solely from their increased release.

The increased levels of cortisol (Table, Vallbano *et al.*, 1966) and vasopressin (Table; Sved *et al.*, 1985) in plasma during the head-up position in tetraplegic

subjects, in addition to other factors including renin and subsequently aldosterone release may reflect, as has been suggested (Claus-Walker *et al.*, 1969; Kamelhar *et al.*, 1978; Kooner *et al.*, 1988), the body's attempt to retain sodium and water to maintain the plasma volume and blood pressure. Direct vasoconstrictor actions of vasopressin and angiotensin II provide an immediate help for the minimisation of orthostatic hypotension during the head-up position of the tetraplegics. On the other hand, there is reason to infer that the increased release of β -endorphin play a pathophysiological role in hypovolemic (Faden and Holaday, 1979) and endotoxic hypotension (Faden and Holaday, 1980), as well as in the hypotension induced by acute transection of the cervical spinal cord (Faden *et al.*, 1980). Thus increased levels of plasma β -endorphin during the head-up position in tetraplegic subjects may contribute, in part, to orthostatic hypotension, or may diminish the restoring effects of the other endocrine reactions. If this is the case, perhaps the use of β -endorphin antagonists, such as naloxone, can improve the ability of the minimisation of orthostatic hypotension during the tilt table treatment of tetraplegics.

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