Desmopressin increases IGF-binding protein-1 in humans

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Abstract

Context: IGF binding protein-1 (IGFBP-1) is essential for IGF-I bioavailability. High levels of IGFBP-1 are encountered in critically ill patients and are a good predictor marker in acute myocardial infarction. The mechanisms responsible for the elevated IGFBP-1 levels in these conditions are still unclear. Interestingly, high levels of vasopressin have been reported in the above-mentioned conditions.

Objective: To study the effect of vasopressin on IGFBP-1 in humans.

Design: Placebo-controlled cross-over study in patients with central diabetes insipidus (CDI) in whom potential interference from endogenous vasopressin secretion is minimized. After a 3-day desmopressin washout period, each patient received i.v. saline on day 1 and desmopressin (3 μg) on day 2. Blood samples were taken after administration, every 2 h during the whole night, starting at 2000 h.

Patients and setting: Fourteen inpatients with CDI in an endocrinology department of a university hospital.

Results: Serum IGFBP-1 increased within 4 h after 1-desamino-8-D-arginine vasopressin (DDAVP) by 375 ± 73%, compared with a spontaneous fasting increase by 252 ± 46% following placebo administration (P < 0.05). No changes were registered in the levels of either classically regulators of IGFBP-1 (insulin, glucagon, and cortisol) or of IGF-I and glucose. The decrease in plasma osmolarity induced by DDAVP did not precede the increase in IGFBP-1.

Conclusions: DDAVP increases serum levels of IGFBP-1. Further investigation is essential to unravel the clinical potential of this interaction in conditions associated with high IGFBP-1 levels.

Materials and methods

Patients

Fourteen inpatients with CDI were included in the study after giving informed consent. The major outcome of the
study has been already published (12). Briefly, nine patients had complete CDI, while five had CDI partially. CDI was diagnosed by water restriction test followed by i.v. injection of 1 μg desmopressin (Ferring, Malmö, Sweden) after 3 h of stable urine osmolality, despite a rising plasma osmolality following fluid restriction (12).

**Study design**
The study protocol was approved by the Ethical Committee of the University of Medicine ‘Carol Davila’ Bucharest. The patients were instructed to discontinue their treatment with desmopressin 3 days before admission to the clinic. At 1900 h, after a standard meal, an indwelling catheter was inserted and at 2000 h each patient received i.v. 1 ml saline in the first evening (day 1) and desmopressin (3 μg; Ferring) in the second evening (day 2). Blood samples were taken at 2-h intervals during the whole night.

**Assays**
The IGFBP-1 levels were measured in the serum using a polyclonal antibody that detects both the phosphorylated and non-phosphorylated forms. The detection limit was 3 ng/ml with inter- and intra-assay coefficients of variation (CVs) of 3 and 10% respectively (2). DDAVP at a concentration up to 4 μg/ml did not cross-react in the IGFBP-1 assay.

The IGF-I serum levels were measured by an RIA after acid–alcohol extraction and cryoprecipitation as described (2). The detection limit was 6 ng/ml with intra- and intra-CVs of 4 and 11% respectively. The insulin levels were measured by an RIA commercial kit (Pharmacia & Upjohn Diagnostics AB) with a detection limit of 2 mU/ml and intra- and inter-CV of 5.8 and 6.4% respectively.

Glucagon concentrations were measured by an RIA commercial kit (Linco Research, St Charles, MI, USA) with a detection limit of 20 pg/ml and intra- and inter-CV of 4.6 and 13.4% respectively. Serum cortisol levels were determined by fluorescence immunoassay (AutoDELFIA, Wallac Oy, Turku, Finland). Intra- and inter-assay coefficients of variation were 4.9 and 6.4% respectively.

Blood glucose was determined by glucose oxidase method using YSI 2300 Stat Plus Analyzer.

**Statistical analysis**
The difference between the levels of the hormones measured after treatments was analyzed by repeated measurement of variance using Statistica 7.1 (StatSoft Inc., Tulsa, OK, USA). Differences of $P<0.05$ were considered significant. The data are represented as mean ± S.E.M.

**Results**

**IGFBP-1**
Mean IGFBP-1 levels (2000 h) were 6.4 ± 1.3 and 8.8 ± 1.9 μg/l before injection of saline and DDAVP respectively. Intravenous injection of 3 μg DDAVP induced a significant increase in IGFBP-1 during the first 4 h, which reached a level of 27.1 ± 8.3 μg/l as compared with the spontaneous night increase after saline 14.3 ± 3.2 μg/l ($P<0.05$; Fig. 1). The IGFBP-1 levels remain higher after DDAVP treatment (43.3 ± 10.1 μg/l) compared with saline (30.5 ± 6.2 μg/l) until the morning (0600 h), however, not statistically significant ($P=0.076$).

**IGF-I and blood glucose and osmolarity**
Mean IGF-I levels were 160.6 ± 40.2 and 177.6 ± 52.9 μg/l before administration of saline and DDAVP respectively ($P=NS$). The serum levels did not change over time 177.6 ± 52.9 and 187.4 ± 57.8 μg/l (2200 h), 202.5 ± 55.5 and 209.3 ± 83.3 μg/l (2400 h) after treatment with saline and DDAVP respectively (Fig. 2A).

No significant changes were found in blood glucose levels during the study: 3.7 ± 0.42 vs 4.6 ± 0.7 mmol/l (2000 h), 3.6 ± 0.4 vs 4.1 ± 0.5 mmol/l (2200 h), 4 ± 0.4 vs 4.1 ± 0.3 mmol/l (2400 h) after saline and DDAVP infusion respectively.

We did not observe any difference in basal osmolarity levels between the 2 days of study (297.17 ± 1.92 vs 292.29 ± 1.97 mOsm/kg). On the other hand, DDAVP decreased the serum osmolarity (287.72 ± 1.99 mOsm/kg at 2400 h).

**Glucagon, insulin, and cortisol**
Desmopressin compared with saline had no effect on the serum levels of either cortisol or insulin. A spontaneous
decrease in the mean concentration of both cortisol (Fig. 2B) and insulin (Fig. 2D) occurred during the first hours of follow-up (P < 0.05). The mean concentration of glucagon did not significantly change and there was no difference between groups (Fig. 2C).

Discussion

We report here for the first time that DDAVP increases IGFBP-1 blood levels. The study was performed on patients with CDI, in a clinical setting where a potential confounding effect from endogenous secretion of AVP is decreased. The increase in IGFBP-1 after DDAVP is specific and is not due to a change in water balance, which would have had an opposite effect through dilution.

Vasopressin acts via three subtypes of receptors that are classified according to the second messenger system to which they are coupled: V1a and V1b (also known as V3) receptors linked to the phosphoinositol signaling pathway and V2 receptors linked to the adenylate cyclase signaling pathway (13). DDAVP, originally developed as a selective agonist for V2 subtype receptors, has been shown to have a similar affinity for V1b receptors (14).

The main source of circulating IGFBP-1 in males and non-pregnant women is the liver where it is produced by hepatocytes (1) that express V1a and V1b receptors (15) but not V2. Thus, DDAVP might induce IGFBP-1 production through a direct liver effect mediated via a V1b-dependent pathway. In agreement with this, in vitro, DDAVP induced an increased IGFBP-1 secretion by HepG-2 cells (human hepatic carcinoma cell line; data not shown). We cannot exclude that DDAVP stimulates IGFBP-1 from other sources as well, such as the kidneys, even though the renal production may not contribute substantially to the circulating IGFBP-1 level (1).

We did not observe a modulation of classical regulators of IGFBP-1 after administration of DDAVP. Nevertheless, due to the sampling schedule, we could not completely reject the possible contribution of some of them. For instance, cortisol has been reported to be stimulated by DDAVP (16). However, the DDAVP effect on cortisol levels lasts less than an hour thus making this explanation less relevant (16). We even observed a
tendency of reduction of the cortisol levels over time following DDAVP injection, even though statistically this was non-significant. This might reflect the dilution effect of the free water retained after DDAVP injection. DDAVP induces also production of catecholamines that, in turn, might result in increased IGFBP-1 serum levels (17). However, it has previously been reported that the effect of catecholamines on IGFBP-1 lasts < 120 min after inoculation (4). Furthermore, DDAVP in doses similar to those used in the present study did not influence epinephrine but only norepinephrine level (17), which has only a marginal effect on IGFBP-1 (4).

We could not detect any difference in the blood levels of glucagon or insulin after injection of DDAVP compared with saline. Even though there is a clear evidence that vasopressin is able to stimulate the secretion of both hormones through V1r receptors (18), it is not surprising that we did not register it, taking into account that the effect is transitional and lasts for less than 60 min.

Injection of DDAVP did not change the concentrations of total IGF-I or glucose. Although IGFBP-1 is an acute regulator of IGF-I bioavailability (1), short-term changes in its blood levels are not always followed by changes in glucose or in total or free IGF-I levels (19).

In conclusion, we demonstrated that DDAVP increases the blood levels of IGFBP-1 suggesting a novel mechanism to explain the high levels of IGFBP-1 observed in critically ill patients or patients with diabetes mellitus. Further investigations are needed to confirm the clinical relevance of our finding.

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