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UREMIC PLASMA, AFTER INFUSION OF DESMOPRESSIN, IMPROVES THE INTERACTION OF NORMAL PLATELETS WITH VESSEL SUBENDOTHELIUM. R. Castillo, G. Escolar, J. Monteagudo, A. Cases, M. Garrido and A. Ordinas. Servicio de Hemoterapia y Hemostasia. Hospital Clínico y Provincial. Universidad de Barcelona.Barcelona.Spain.

Desmopressin (DDAVP) shortened the bleeding time and increased the platelet retention on glass beads and the platelet interaction on subendothelium measured by the Baumgartner perfusion system in 11 uremic patients in whom the three tests were abnormal previous to the treatment (1).

Patients were chosen at random out of a group of 30 with prolonged bleeding time and decreased platelet retention on glass beads. All tests were performed on blood drawn before and one and six hours after a single dose of DDAVP (0.4 μg/kg body weight). Perfusion experiments were carried out at a shear rate of 800 sec^{-1}.

Levels of VIII:C, VIIIR:Ag and RiCof were at the upper limit of normality before DDAVP and significantly increased one hour after treatment. The multimeric structure of vWF in pretreatment plasma was normal ; one hour after DDAVP larger multimers appeared.

After injection of DDAVP, the perfusion studies using reconstituted blood with uremic PPP in presence of isolated normal platelets and washed red cells, showed a statistically increased surface coverage and platelet aggregate formation on subendothelium ($p < 0.05$ respectively when compared to the pretreatment values). In the same perfusion assays, the in vitro addition to pretreatment plasmas of 1 u/ml of purified vWF with normal multimeric structure, or purified VIII:C and vWF (1 u/ml each) did not modify the decreased platelet interaction on subendothelium.

These results confirm the shortening of bleeding time by DDAVP in uremic patients and reveal an increase of platelet interaction on vessel subendothelium mediated by a factor present in PPP. Besides, they show that the effect of DDAVP in these patients is not due to the quantitative increase of the plasmatic vWF and FVIII.

(1) Blood, 68, 2:337-342, 1986.

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THE EFFECTS OF VASOPRESSIN ON FIBRINOLYSIS AND FACTOR VIII ARE NOT MEDIATED THROUGH V_2 RECEPTORS. P.J. Grant, K.K. Hampton, P.G. Wiles and C.R.M. Prentice. University Department of Medicine, The General Infirmary, Leeds. LS1 3EX, UK.

Vasopressin (aVP) mediates its effects on smooth muscle through V_1 receptors and on the kidney via pharmacologically distinct V_2 receptors. Infusions of aVP and its long acting synthetic analogue DDAVP both produce increases in factor VIII and fibrinolytic activity in man. V_1 receptors are known not to mediate this effect, however it has been suggested that the FVIII response might be mediated by V_2 receptors as patients with nephrogenic diabetes insipidus are reported to have no FVIII response to DDAVP. It remains unclear whether this is a true phenomenon or reflects tachyphylaxis to the high vasopressin levels found in nephrogenic diabetes insipidus. The aim of this study was to investigate whether the pharmacological V_2 receptor blocker lithium alters the effect of aVP infusions on FVIII and fibrinolysis in man. 4 control subjects and 6 patients taking long term lithium therapy (mean serum lithium 1.09 mmol/l) were infused with 2.0 units aVP over 1 hour. Samples were collected for assay of aVP, euglobulin clot lysis time (ECLT) and FVIII coagulant activity (FVIIIC) before and at the end of infusion. In the control subjects median aVP rose from 0.5 to 83 pg/ml at the end of infusion. FVIIIC rose from 100 to 333% and plasminogen activator activity (PAA: 10^6/ECLT) from 198 to 437 units. In the lithium treated group median aVP rose from 0.5 to 68 pg/ml at the end of infusion. FVIIIC rose from 100 to 263% and PAA from 102 to 453 units. There was a significant correlation between the plasma aVP and FVIIIC ($r = 0.89$ $p < 0.005$) and PAA ($r = 0.92$ $p < 0.001$) in the control group and the lithium treated group (FVIIIC $r = 0.81$ $p < 0.002$; PAA $r = 0.69$ $p < 0.02$). There was no significant difference between the rise in either FVIIIC or PAA in the lithium treated group compared with controls. These results do not support the hypothesis that the action of aVP on FVIII or fibrinolysis is mediated by V_2 receptors. The effects of aVP on haemostasis may either be mediated directly through a third class of receptor or indirectly by the release of an intermediate hormone.

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EVIDENCE FOR PLASMIN-MEDIATED FIBRINOLYSIS AFTER RELEASE OF TISSUE PLASMINOGEN ACTIVATOR BY DESMOPRESSIN INFUSION. G.D.O Lowe (1), J.T. Douglas (1), M. Small (1), C. Kluft (2), C.D. Forbes (1). University Department of Medicine, Royal Infirmary, Glasgow, U.K.(1); and Gaubius Institute TNO, Leiden, The Netherlands (2).

A relationship between tPA activity and plasmin-mediated fibrinolysis in vivo (plasma levels of Bβ15-42-containing peptides) has been suggested by our previous studies: inverse correlations of Bβ15-42 levels with obesity and triglyceride levels (both associated with high tPA inhibition) in an epidemiological study; and increased levels of Bβ15-42 following improved control of diabetes, or treatment with oral or intramuscular stanozolol (which decrease tPA inhibition). The aim of the present study was to establish whether or not intravenous infusion of desamino-D-arginine vasopressin (DDAVP, desmopressin) is followed by increases in plasmin-mediated fibrinolysis in vivo (plasma Bβ15-42 levels). Desmopressin (0.3 μg/kg body weight) was infused intravenously over 15 mins in 22 subjects. Venous blood was obtained by separate venepuncture before and 15 mins after the end of the infusion, for assay of plasminogen activator activity of the euglobulin fraction on fibrin plates, tPA activity, and Bβ15-42 levels (RIA,IMCO). 18 subjects showed normal increases in fibrin plate lysis and in tPA activity after desmopressin (median tPA activity 120 mU/ml pre-, 5000 mU/ml post-infusion, $p<0.001$). In these 18 subjects, Bβ15-42 levels rose significantly (median 1.5pmol/ml pre-, 4.2 pmol/ml post-infusion, $p<0.001$). Four subjects showed no significant increases in fibrin plate lysis or in tPA activity after desmopressin (non-responders): all had significantly elevated levels of tPA-inhibition. In these 4 subjects no increases in Bβ15-42 levels were observed. In one non-responder, who suffered a large myocardial infarction due to angiographic thrombosis with no atheroma at the age of 22 years, long-term treatment with stanozolol normalised the high level of tPA-inhibition, as well as the fibrin plate lysis and tPA activity responses to desmopressin: Bβ15-42 level then showed a normal response after desmopressin infusion (2.2 to 5 pmol/ml). We conclude that desmopressin infusion increases plasmin-mediated fibrinolysis in vivo, but only in the presence of normal increases in tPA activity.

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THE RESPONSE OF PROTEIN S, TISSUE PLASMINOGEN ACTIVATOR AND TISSUE PLASMINOGEN ACTIVATOR INHIBITOR TO DESMOPRESSIN (DDAVP) INFUSION. N. K. Wadhwa, S. Kim, P. Glas-Greenwalt, K. S. Kant, and V. E. Pollak. University of Cincinnati Medical Center, Cincinnati, Ohio, U.S.A.

Protein S (PS) is a cofactor for activated protein C (PC) in the neutralization of tissue plasminogen activator inhibitor (PA-I) and in its profibrinolytic effect (Blood 69:231, 1987). Increased fibrinolytic activity and tissue plasminogen activator (t-PA) antigen in response to venous occlusion are dissociated because of t-PA and PA-I complex formation (Br. J. Haematol. 61:169, 1985). We hypothesized that DDAVP infusion stimulates t-PA and PS release from endothelium, thereby decreasing PA-I. These responses to intravenous DDAVP infusion (0.4 μg/kg) were studied in 10 healthy volunteers. t-PA activity and PA-I were measured by standard fibrin plates. t-PA antigen was assayed by ELISA. PS and PC were measured by electroimmunodiffusion. The baseline values were expressed as 100%. Mean values expressed as percent of baseline at 10, 30, 60 min after DDAVP infusion were:

Time	t-PA	t-PA antigen	PS	PC	PA-I
Pre	100	100	100	100	100
10	385**	298**	136**	96	82*
30	407**	278**	120**	90	76*
60	281**	186**	142**	95	87*

*p <0.05; **p <0.005 (one-way ANOVA test)

These data support that both t-PA and PS were released, during DDAVP infusion, thereby resulting in decreased PA-I.