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A NEW VASOPRESSIN ANALOGUE AND FIBRINOLYSIS

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Summary In five healthy men an intravenous dose of 10 μg. of 1-desamino-8-D-arginine vasopressin (D.D.A.V.P.) stimulated a rapid systemic release of plasma-plasminogen-activator. Unlike the responses recorded with lysine vasopressin and arginine vasopressin, the response to D.D.A.V.P. was protracted and devoid of side-effects. The magnitude of the D.D.A.V.P.-induced release of plasminogen activator was similar to that associated with moderate exercise and intravenous adrenaline.

INTRODUCTION

THE mechanisms responsible for the release of stored plasminogen activator, an essential precursor enzyme in the fibrinolytic-enzyme system, from the endothelial cells are unknown, although recent studies in man have suggested that catecholamines may play an important role.[1] Earlier animal studies implied that the vasoactive effect of vasopressin was associated with a non-specific release of plasminogen activator.[2-4] Mannucci and Barbi confirmed that plasminogen activator in man is released after intravenous lysine vasopressin.[5] This observation is difficult to interpret, since Mannucci and Barbi noted that the fibrinolytic response seemed to be closely associated with the presence and severity of side-effects, especially abdominal pain and an intense desire to defæcate.

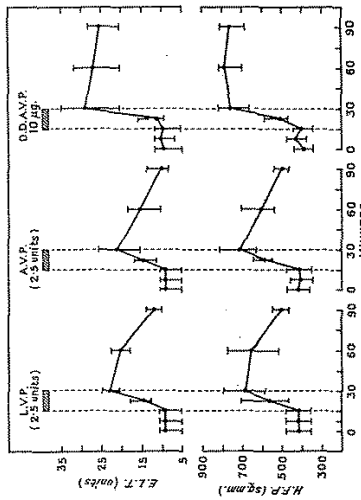

Fig. 1—Plasma-plasminogen-activator responses to L.V.P., A.V.P., and D.D.A.V.P. using the E.L.T.s and H.F.P. assays in 5 healthy men.

Closed circles represent arithmetical means and the vertical bars the complete range.

Such unpleasant symptoms raised the possibility that the observed fibrinolytic response was more likely to be related to a stress-induced release of endogenous catecholamines than a specific vasopressin effect.

The introduction of a new analogue of vasopressin, 1-desamino-8-D-arginine vasopressin (D.D.A.V.P.), in which the hemicysteine in position 1 has been replaced by β-mercaptopropionic acid and the L-arginine in position 8 by D-arginine, is of both theoretical and practical interest. The change in position 1 enhances the antidiuretic activity of the molecule,[6] and that in position 8 substantially reduces pressor activity.[7] In volunteers and clinical studies, intravenous D.D.A.V.P. in doses up to 16 μg. was without side-effects [8] and produced, unlike the evanescent response of lysine vasopressin (L.V.P.), a sustained antidiuretic action, due to the slow metabolic clearance of D.D.A.V.P.[9]

We describe a series of studies in which the plasminogen-activator response to infusions of synthetic L.V.P., A.V.P., and D.D.A.V.P. was examined in volunteers.

METHODS

The five subjects were healthy male colleagues (aged 28–36 years) who were fully conversant with the aims and objectives of the proposed experiments. All procedures were performed between 9 and 11 A.M., and before the infusions the subjects remained supine for 30 minutes. The infusions (2·5 units L.V.P. and A.V.P. and 10 μg. D.D.A.V.P., made up in 25 ml. saline solution) were introduced via a 15-gauge needle, using a Harvard constant-infusion pump, into a cubital-fossa vein over a period of 15 minutes. This was preceded by a 15-minute control period, during which saline was infused (25 ml.). Serial blood-samples were obtained from a similar vein in the contralateral limb through an indwelling 15-gauge needle whose patency was maintained by a constant infusion of saline (1 ml. per minute). The plasma-plasminogen-activator content was assayed using the euglobulin-lysis time (E.L.T.) and human-fibrin-plate (H.F.P.) techniques described elsewhere.[10] Pulse-rates were recorded continuously with an electrocardiogram and arterial blood-pressures were measured at 5-minute intervals by a sphygmomanometer. A t test was used to compare the values of the three pre-infusion with the three subsequent blood-samples.

RESULTS

The results are summarised in fig. 1. There was a significant release of plasminogen activator, as assessed by both the E.L.T. and H.F.P. techniques for L.V.P. ($P<0.005$), A.V.P. ($P<0.005$), and D.D.A.V.P. ($P<0.005$).

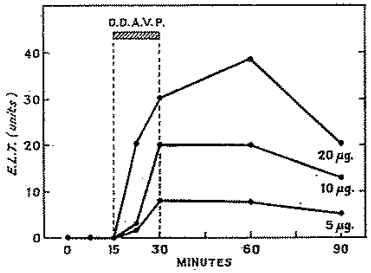

Fig. 2—Plasma-plasminogen-activator responses in a healthy man receiving increasing doses of D.D.A.V.P.

The fibrinolytic response to D.D.A.V.P. was more extended than that following L.V.P. and A.V.P. and was not associated with side-effects, whereas both L.V.P. and A.V.P. induced mild abdominal pain and pronounced cutaneous pallor in all five subjects. There were no significant changes in the pulse-rate or blood-pressure during or after the infusion of all three vasopressin preparations. A dose/response phenomenon was observed with D.D.A.V.P. (fig. 2).

DISCUSSION

The results of the present preliminary study support the findings of Mannucci and Barbi,[5] who found that vasopressin will stimulate a release of circulating plasminogen activator in man. The positive response to D.D.A.V.P., which has only slight vasoactive properties and is devoid of intestinal side-effects, suggests that at least part of the fibrinolytic response to L.V.P. and A.V.P. is unlikely to be secondary to direct vasoactive phenomena or the release of endogenous catecholamines associated with psychological stress. Unlike the evanescent response to L.V.P. and A.V.P., the enhanced fibrinolytic potential to D.D.A.V.P. was sustained and thus parallels the time sequence of the antidiuretic response of this preparation. The magnitude of the D.D.A.V.P.-induced fibrinolytic response was similar to that observed in earlier studies in our laboratory after moderate exercise and intravenous adrenaline.[11] Although the fibrinolytic response to

vasopressin is likely to be specific, there is insufficient data to postulate the existence of specific vasopressin receptors in the endothelial cell.

While it is probable that the results of our investigations contribute to the further understanding of the physiological control of fibrinolysis, the fact that D.D.A.V.P. induced a rapid and sustained release of plasminogen activator may have important therapeutic implications. D.D.A.V.P. is currently being introduced in the long-term management of cranial diabetes insipidus,[8] and it seems reasonable to hope that studies of other vasopressin analogues may give rise to a family of compounds without antidiuretic, vasoactive, or intestinal activity, but with potent and extended potential for stimulating fibrinolysis.

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