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Normal Fibrinolytic Responses to 1-Desamino-8-D-Arginine Vasopressin in Patients with Nephrogenic Diabetes insipidus Caused by Mutations in the Aquaporin 2 Gene

Key Words

Nephrogenic diabetes insipidus
 Aquaporin 2
 1-Desamino-8-D-arginine
 vasopressin
 Tissue-type plasminogen activator
 Vasopressin type 2 receptor

Abstract

Three patients with autosomal-recessive nephrogenic diabetes insipidus (NDI), homozygous for mutations in the aquaporin 2 gene (AQP2), were tested for their fibrinolytic and hemodynamic responses to intravenous administration of 1-desamino-8-D-arginine vasopressin (DDAVP). They all showed an increase of tissue-type plasminogen activator antigen, facial flushing, an increase of heart rate and a decrease of diastolic blood pressure. These results confirm the hypothesis that NDI patients with an AQP2 defect can be discriminated from NDI patients with a vasopressin type 2 receptor defect by their normal extrarenal responses to DDAVP.

Introduction

The main functions of the neurohypophyseal hormone arginine vasopressin (AVP) are reflected by its two names; 'vasopressin' refers to the vasoconstriction resulting from binding to vasopressin type 1 receptors on vascular smooth muscle cells, while 'antidiuretic hormone' designates the urinary concentration occurring in response to binding to vasopressin type 2 (V2) receptors in the renal collecting ducts. Strong activation of the V2 receptor can be accomplished by administration of 1-desamino-8-D-arginine vasopressin (DDAVP), a V2 receptor agonist with an antidiuretic/pressor ratio of 4,000 [1]. In addition to its renal antidiuretic action, DDAVP elicits vasodilation and an increase of coagulation and fibrinolysis factors [2, 3]. The exact location of the V2 receptors which mediate these effects is unknown. Studies in anephric subjects have excluded the possibility that they are situated in the kidney [2, 4]. Moreover, evidence supporting the presence of V2 receptors on monocytes has been gained [5, 6]. Hereditary nephrogenic diabetes insipidus (NDI) is a rare disease in which the antidiuretic response to AVP and DDAVP is lacking, resulting in polyuria,

polydipsia and an increased risk of dehydration. Furthermore, most NDI patients lack the extrarenal responses to DDAVP, indicating a generalized V2 receptor defect [3, 7-9]. Evidence for the hypothesis that a V2 receptor defect causes NDI was gained when mutations in the V2 receptor gene were found in patients with the X-linked recessive form of the disease [10]. Some patients have been reported, however, who showed normal fibrinolytic, coagulation and hemodynamic responses to DDAVP, indicating that their extrarenal V2 receptor functions normally [11-13]. The observation that, in these patients, only the renal response to DDAVP is impaired, can be explained by the presence of a defect in the antidiuretic AVP pathway beyond the V2 receptor. Recently, the gene was cloned which encodes the aquaporin 2 (AQP2) water channel, a protein that is inserted into the apical membrane of collecting duct cells in response to activation of the V2 receptor [14]. The first patient in which we observed a normal extrarenal response to DDAVP was demonstrated to be a compound heterozygote for mutations in this autosomal AQP2 gene, a finding which confirmed the postulated presence of a renal post-V2-receptor defect [15]. Since this is the only patient with a proven

AQP2 defect whose extra-renal responses to DDAVP have been studied, we performed DDAVP tests in 3 additional patients with distinct AQP2 mutations, with the objective of confirming the assumption that in these NDI patients extrarenal responses to DDAVP are normal.

Methods

Patients

DDAVP tests were performed in 3 NDI patients in whom homozygosity for an AQP2 mutation had been detected by sequencing analysis (table 1). All patients gave informed consent prior to the test. A detailed description of the case histories, DNA analysis and in vitro expression of the mutations has been given in a previous report [16]. Patients 1 and 3 did not take any medication. Patient 2, who used amiloride-hydrochlorothiazide 2 times a day, discontinued medication 12 h prior to the test.

DDAVP Tests

Food and water were not restricted before or during the test. After cannulation of a cubital vein, patients rested for 50 min in the recumbent position. From $t = 0$ to $t = 10$, a dose of $0.3 \mu\text{g}$ DDAVP (Minirin®, Ferring, Malmö, Sweden) per kg body weight, diluted in 100 ml NaCl 0.9%, was infused. Systolic and diastolic blood pressure and heart rate were monitored at 3-min intervals during the first 25 min and at 10-min intervals thereafter. Blood samples were taken from the indwelling venipuncture 10 min before ($t = -10$), immediately before ($t = 0$) and 10, 20, 30 and 60 min after the start of the DDAVP infusion. Each time the first 4 ml of blood were discarded. The next 4.5 ml were collected in a new syringe and transferred into tubes containing 0.5 ml 3.8% sodium citrate. The tubes were immediately cooled on melting ice. Platelet-poor plasma obtained by centrifugation at 4°C for 10 min at 3,000 g, was quickly frozen in aliquots of 0.5 ml and stored at -70°C until assays were performed. Tissue-type plasminogen activator antigen (tPA:Ag) was measured by an enzyme-linked immunoassay (Innotest, Chromogenix, Zwijndrecht, Belgium). Data were compared with those obtained from 6 NDI patients [3] in whom a V2 receptor gene mutation had been found.

Results

In the 3 patients with an AQP2 defect, a significant rise of tPA:Ag values occurred in response to the DDAVP administration. The intensity and time course of the responses varied, but the pattern was clearly distinct from those obtained in patients with a V2 receptor defect (fig. 1). Furthermore, a few minutes after the start of the DDAVP infusion, an increase of heart rate, varying from 29 to 48% compared to the baseline heart rate ($t = 0$), and a facial flush were observed. During the DDAVP infusion, all patients showed a decrease of diastolic blood pressure (15–22%) compared to the baseline value. No significant decrease of systolic blood pressure was observed (3–9%) (data not shown).

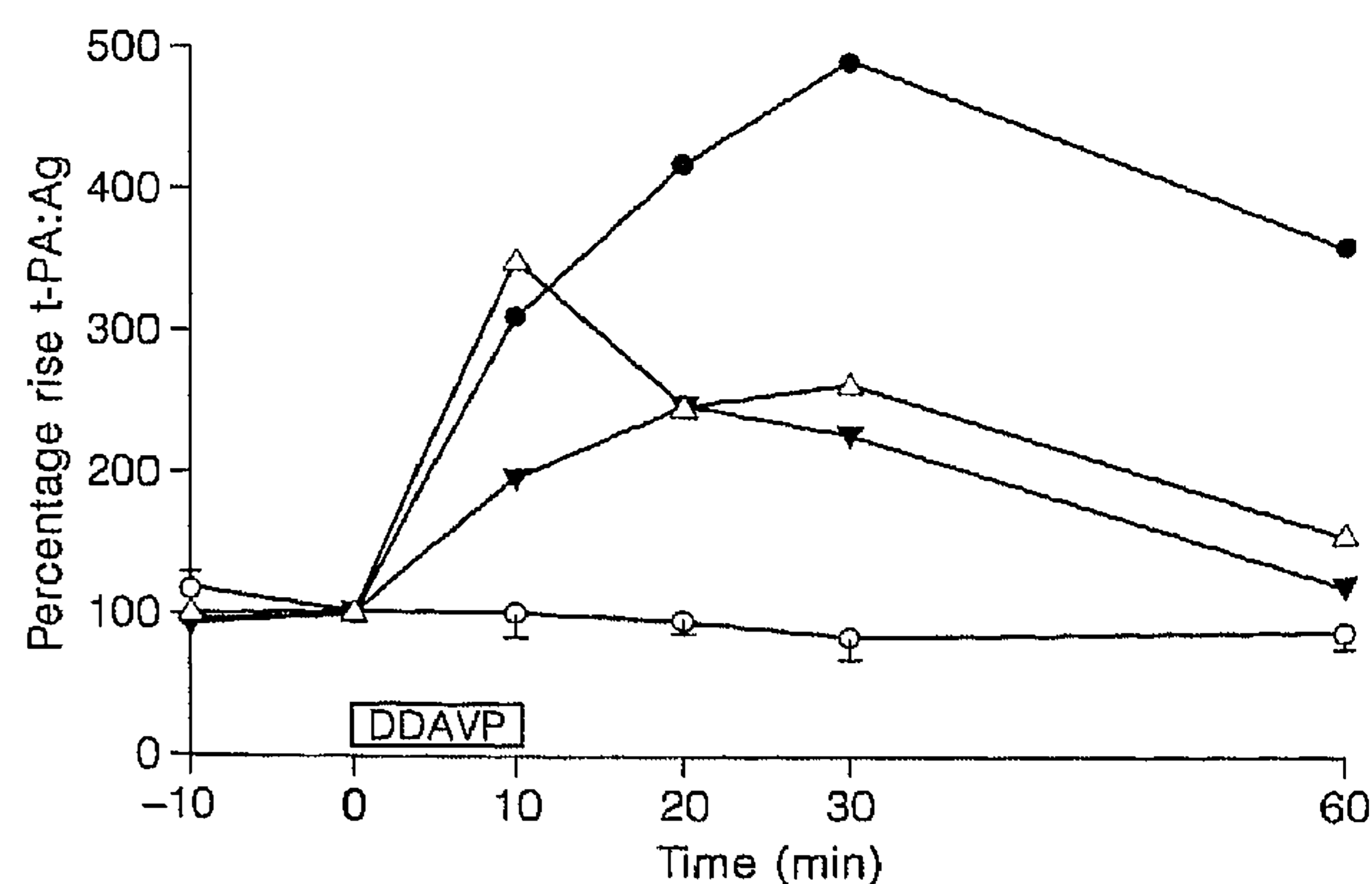


Fig. 1. Tissue-type plasminogen activator antigen response (tPA:Ag) to DDAVP in the 3 patients studied (● = patient 1; Δ = patient 2; ▼ = patient 3). Mean and SEM values of 6 NDI patients [3] with a V2 receptor mutation (x) are shown as well. tPA:Ag values at $t = 0$ are expressed as 100%.

Table 1. Data on NDI patients with an AQP2 defect

Patient No.	Age, years	Sex	Mutation
1	29	M	Arg187Cys
2	25	F	Gly64Arg
3	18	M	C369del

Discussion

Two genetically distinct forms of hereditary NDI are currently known to exist; X-linked NDI is caused by mutations in the V2 receptor gene, autosomal-recessive NDI results from mutations in the AQP2 gene. The clinical phenotype in these two categories of patients seems identical [16], rendering discrimination between the two forms on this basis impossible. Observations made in the first-described AQP2-NDI patient, however, suggested that these patients may be distinguished from patients with a V2 receptor defect by means of their extrarenal responses to DDAVP [12, 15]. The present study confirms this hypothesis by demonstrating an increase of tPA:Ag and heart rate, a decrease of diastolic blood pressure and the occurrence of a facial flush in 3 additional NDI patients with an AQP2 defect. Discrimination of the two subgroups of NDI patients on the basis of a DDAVP test is useful in families in which only 1 patient or several siblings are affected, since in these families the nature of the genetic defect cannot be inferred from the pattern of

inheritance. In these families, results of the test permit a more efficient approach for DNA analysis. Moreover, in circumstances where facilities for DNA analysis are lacking, they may provide the sole basis for genetic counselling.

When performed in female patients, interpretation of the test is more complicated. Although in female patients an AQP2 defect seems obvious, we observed a phenotype similar to the phenotype of male NDI patients, including absence of the extrarenal response to DDAVP, in female carriers of a V2R mutation [17]. A plausible explanation for this phenomenon is predominant inactivation of the X-chromosome carrying the normal V2R allele in both renal collecting duct cells and cells mediating the extrarenal response to DDAVP. Since patterns of X-inactivation have been described to vary between different tissues [17], it is possible that the extrarenal response to DDAVP is normal in some of the symptomatic female carriers of a V2 receptor mutation. This could be the case, for instance, in the female patients described by Brenner et al.

[11] and Moses et al. [18]. Therefore, it seems hazardous to discriminate female NDI patients homozygous for an AQP2 mutation from female patients hemizygous for a V2 receptor gene mutation on the basis of a normal extrarenal DDAVP test. Absence of this response, however, appears to be a distinguishing feature.

In conclusion, normal extrarenal responses to DDAVP have now been demonstrated in 4 NDI patients with a proven AQP2 defect, thereby confirming that this test can discriminate between male AQP2 patients and male V2 receptor patients. In female patients with a normal response, however, the possibility that hemizyosity for a V2 receptor mutation causes the disease needs to be considered.

Acknowledgements

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Addendum:

Recently, the female patient described by Moses et al. [18] has indeed been found to be heterozygous for a V2 receptor mutation: Moses AM, Sangani G, Miller JL: Proposed causes of marked vasopressin resistance in a female with an X-linked recessive V2 receptor abnormality. *J Clin Endocrinol Metab* 1995;80:1184–1186.