Rolipram, a Phosphodiesterase Inhibitor, in the Treatment of Two Male Patients with Congenital Nephrogenic Diabetes insipidus

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Dear Sir,

Congenital nephrogenic diabetes insipidus is a rare X-linked disorder characterized by renal and extrarenal resistance to the administration of the antidiuretic hormone arginine vasopressin [1]. The antidiuretic action of vasopressin is mediated through the binding of vasopressin to its receptors and the sequential receptor-mediated stimulation of the release adenylate cyclase. Guanine nucleotide-binding proteins also intervene in this transduction process [2]. We recently proposed that a precyclic adenosine monophosphate (AMP) V₂ receptor-defective mechanism was involved in patients with congenital nephrogenic diabetes insipidus since l-desamino[8-D-arginine]vasopressin (dDAVP), a V₂-receptor agonist, administration increased plasma cyclic AMP concentrations in normal subjects but not in 14 male patients with congenital nephrogenic diabetes insipidus [3]. Intermediate responses were observed in obligatory carriers. A downregulation of the V₂ receptors was likely not involved, since the plasma vasopressin concentrations were identical in normal subjects and obligatory carriers and only slightly elevated in affected males (4.2 ± 1.0 pg/ml or 4.5 ± 1.08 pmol/l).

In mice with hereditary nephrogenic diabetes insipidus (a non-X-linked hereditary disorder in mice), the increase in the water permeability of the collecting duct in response to the administration of arginine vasopressin is inadequate [4]. In these mice, the activity of cyclic AMP-phosphodiesterase, which prevents the accumulation of the intracellular mediator cyclic AMP, is also increased [5]. The incubation of the inner medullary collecting ducts of mice with nephrogenic diabetes insipidus with two inhibitors of cyclic AMP-phosphodiesterase isoenzyme type III (Rolipram and Cilostamide) completely restored the cyclic AMP accumulation in response to vasopressin administration [6]. The administration of Rolipram has also been shown to increase urinary osmolality and to correct the high fluid turnover in these animals [7]. The pathophysiological mechanism underlying the mouse model of hereditary nephrogenic diabetes insipidus (increased cyclic AMP catabolism) seems then to be different from its human counterpart (a precyclic AMP defect).

To distinguish between these two mechanisms, we studied two brothers (29 and 31 years old) with congenital nephrogenic diabetes insipidus and typical X-linked inheritance. In both, the

documented water intake was larger than 8 liters/day and both were resistant to vasopressin or dDAVP administration, i.e., the administration of dDAVP did not stimulate the release of the coagulation factors and plasma cyclic AMP or the plasma renin activity [1,3]. Both had repeated and prolonged episodes of dehydration during their 1st year of life and have been left with some degree of mental retardation. Rolipram (from 3×0.25 to 3×1 mg/day, dosage was doubled every 2 days) was administered for a total of 7 days. Four consecutive 30-min morning urinary collections were made during the first 4 days and the last day of testing (total of 5 days, 20 collections/patient). Creatinine, osmolar and free water clearances were calculated. Plasma and urinary cyclic AMP excretion rates were measured by radioimmunoassay as previously described [3].

No untoward effects were observed. Urinary osmolality was unchanged (less than 200 mosm/kg or 200 mmol/kg) as well as free water and osmolar clearances. Urinary cyclic AMP excretion rates (0.95 ± 0.07 $\mu\text{g}/\text{min}/1.73 \text{ m}^2$ or 2.9 ± 0.2 nmol/min/ 1.73 m^2) and plasma cyclic AMP

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concentrations (26.5 ± 2.2 pg/ml or 80.4 ± 6.7 pmol/l) also remained unchanged during the entire observation period; similar values were obtained in 12 other male patients with congenital nephrogenic diabetes insipidus studied in our laboratory [3]. These results suggest that the mouse defect in cyclic AMP catabolism is probably not present in humans with congenital X-linked nephrogenic diabetes insipidus.

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