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Chronic Cystitis: Excretion of Epidermal Growth Factor (EGF)/ Urogastrone (URO)

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Summary. To investigate the role of epidermal growth factor (EGF)/urogastrone (URO) in the cytoprotection of the urothelium in the urinary bladder we measured the concentration of EGF/URO by radioimmunoassay in urine from patients with chronic cystitis. The series comprised 12 patients with classical interstitial cystitis, 10 young females with recurrent bacterial cystitis and 12 children with recurrent cystitis together with sex- and age-matched controls. The results showed no variation in the substance concentration of EGF/URO in urine from cystitis patients and control groups. A negative correlation was found between 1) the urinary concentration of EGF/URO and increasing age, and 2) the excretion of EGF/URO per mol creatinine. The present study did not show a decreased output of EGF/URO in patients with chronic cystitis. Further studies are necessary in the evaluation of the physiological role of EGF/URO in the urinary tract.

Key words: Cystitis, Epidermal growth factor, Urogastrone.

Introduction

The natural defense mechanism of the bladder against bacteria is complex and incompletely understood. However, an intact bladder epithelium is an essential factor.

In different types of chronic or recurrent cystitis the underlying defect remains obscure. It may be assumed that the natural intrinsic resistance of the bladder epithelium is destroyed [15] and defective cytoprotection results. It has been proposed that patients with interstitial cystitis have defective, leaky urothelium and a defective glycosaminoglycans (GAG) layer [15, 16]. The GAG-layer is also thought to be defective in patients with chronic or recurrent bacterial cystitis [1].

Epidermal growth factor (EGF) or urogastrone (URO) is a potent growth stimulating hormone. In vitro and in vivo experiments have shown that EGF/URO promotes cell proliferation and differentation, DNA and RNA synthesis in cells and the synthesis of hyaluronic acid and other glycosaminoglycans. Therefore, EGF/URO might play a role in the protection and maintenance of internal epithelium in the gastrointestinal and urinary tracts [7, 14].

Furthermore, it has been shown recently that EGF/URO is produced by the kidneys and is excreted into the urine [13]. Therefore, it is reasonable to hypothesize that a decreased production of EGF/URO in the urinary tract may be involved in the pathogenesis of cystitis.

In the present study we measured the concentration of EGF/URO in urine in patients of different age and with different types of chronic cystitis and compared the results with sex- and age-matched controls.

Materials and Methods

The material comprises 3 groups of out-patients with chronic cystitis and matched control groups.

I: Twelve female patients with interstitial cystitis had severe daytime frequency, nocturia (2–16 times/night), urgency and supra-retropubic pain despite sterile urine. Some of these patients also had dysuria and hematuria. The symptoms had persisted for more than one year. Cystoscopy revealed petechial bledding after bladder distension for 1 min.

These features were taken as diagnostic of classical interstitial cystitis [9]. Bladder biopsies from all 12 patients showed detrusor mastocytosis (more than 28 mast cells/mm^2), a histological criterion proposed for interstitial cystitis [8]. No patient received drug therapy at the time of urine collection.

II: Ten females with recurrent bacterial cystitis underwent normal i.v. pyelography, normal urodynamic investigation, normal gynecological examination and a normal cystoscopy. All patients had more than three positive urinary cultures with significant bacterial growth ($> 10^5$ *E. coli*/ml) within the last year. These patients were asymptomatic, were not taking medication and had negative urinary cultures during the month prior to the collection of urine.

III: Twelve girls with recurrent bacterial urinary tract infection were characterized clinically in the same way as the young females.

The three control groups were age-matched ± 5 years (children ± 3 years) in each group.

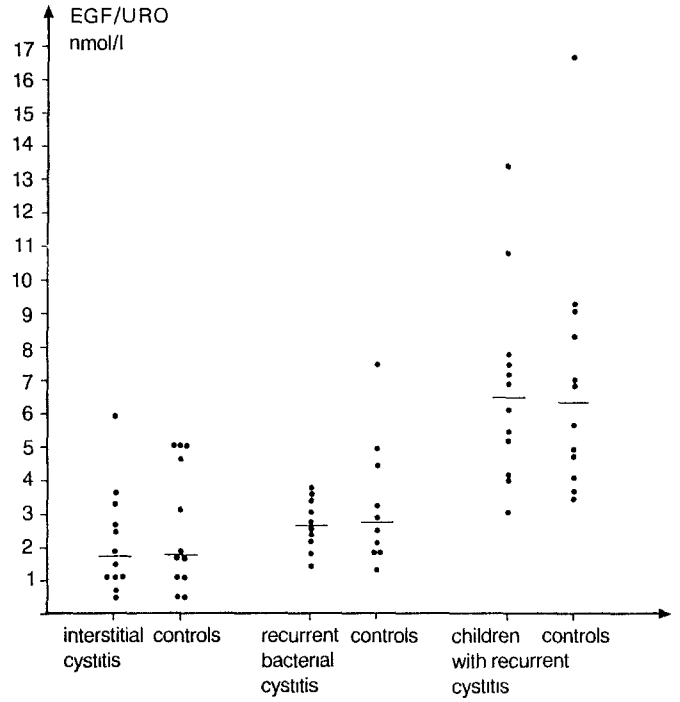

Fig. 1. Substance concentration of EGF/URO in urine from patients with chronic cystitis and controls. Median values are shown

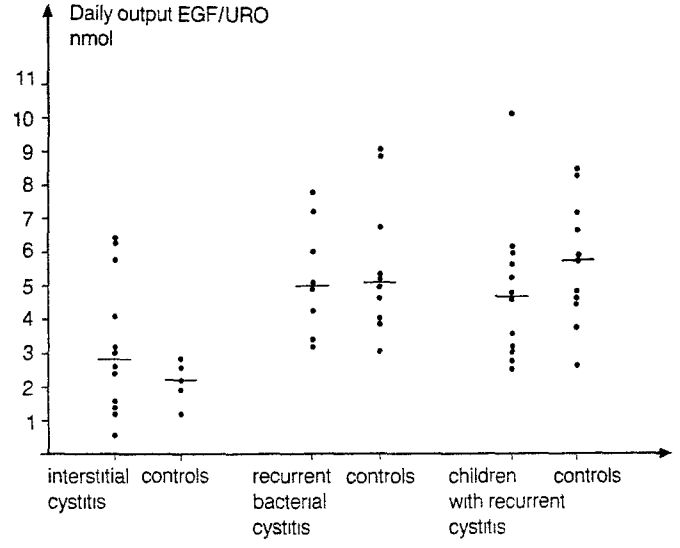

Fig. 2. Total daily output of EGF/URO in urine from patients with chronic cystitis and controls. Median values are shown

Urine Analyses

The urine was collected over 24 h and samples were taken and analyzed by radioimmunoassay for human EGF/URO.

Assay design has been described previously [10, 12]. The antibody was raised in rabbits against pure human urinary EGF [11, 12].

Antibody 1589 in final dilution 1:37.500 was employed together with ^{125}I synthetic urogastrone (10^6 Cpm/pmol) as tracer and purified human urinary EGF [11] as calibrator. The sensitivity of the assay was 0.08 nmol/l and the precision was 9% ($\bar{x}$ = 0.83).

Synthetic human urogastrone was a gift from H. Gregory, ICI.

The substance concentration of creatinine in urine was quantitated on an automatic analyzer (SMAC, Technicon) from the color reaction with picrinic acid.

The total daily output of EGF/URO was calculated as was the excretion of EGF/URO per mol creatinine.

Statistics

Statistical analyses were performed with a Mann-Whitney rank sum test.

Results

The concentration of EGF/URO in urine was the same within each cystitis group compared to their respective control group ($p > 0.05$) (Fig. 1).

The concentration of EGF/URO in urine was the same for the interstitial cystitis group and for the recurrent bacterial cystitis group ($p > 0.05$) but the concentration of EGF/URO in urine from children with cystitis was significantly higher than in the two adult cystitis groups ($p < 0.01$) (Fig. 1).

The total daily output of EGF/URO in urine was calculated and no difference between each cystitis group and their controls was found ($p > 0.05$) (Fig. 2). The interstitial cystitis patients had a significantly lower total daily output of EGF/URO in urine than the two other groups ($p < 0.05$) (Fig. 2). Table 1 shows the excretion of EGF/URO per mol creatinine in the three groups and this parameter was significantly higher in children than in the two other groups ($p < 0.01$).

Discussion

EGF/URO was discovered in 1962 [2] and purified from mouse submandibular glands in 1974 by Cohen [3]. It is a potent growth stimulating hormone. It has been found to be identical to β-urogastrone purified from human urine by Gregory [5]. The excretion of EGF/URO in human urine shows no diurnal or postprandial variations [4], nor any relation to the menstrual cycle [6].

The excretion is under multihormonal control (thyroid hormones, androgens and adrenal cortical hormones) [17]. Furthermore, the excretion correlates with urinary excretion of creatinine and with increasing age the excretion of EGF/URO decreases [17].

Two observations have initiated the present work. It is recently shown that EGF/URO is produced in the kidneys and excreted from the kidneys into the urine [13]. Parenteral and oral administration of EGF/URO has a preventive and healing effect on experimentally produced ulcers in the gastrointestinal tract [7, 14], and thus EGF/URO is of importance in the cytoprotection of the alimentary tract. Therefore, it was obvious to speculate a role for EGF/URO in connection with maintenance of a normal epithelial surface also in the urinary tract, especially in the bladder.

Table 1. The excretion of EGF/URO per mol creatinine in patients with chronic cystitis and controls

	No. of patients	Median age years	Range years	Excretion of nmol EGF/URO per mmol creatinine median (range)
Interstitial cystitis	12	56.5	37–79	0.26 (0.13–0.58)
Controls	12	52	33–74	0.32 (0.27–0.39)
Recurrent bacterial cystitis	10	30	24–40	0.38 (0.27–0.57)
Controls	10	29	20–40	0.49 (0.28–0.82)
Children with recurrent cystitis	12	9	5–13	1.08 (0.46–1.73)
Controls	12	9.5	7–13	0.91 (0.51–1.36)

However, the results of the present study did not show what we expected to find, namely, a decreased output of EGF/URO in the patients with different types of chronic cystitis compared to controls.

An obvious explanation to this is that the hypothesis was wrong and that EGF/URO is without any importance in the urinary tract as compared to the gastrointestinal tract.

Another explanation could be that the concentration of EGF/URO in urine from these patients is normal, but the hormone is unable to elicit its effect on the target organ, i.e. the urothelial cells, possibly because of a defect or block in the receptor.

A third possibility is a type 2-error since the variation in EGF/URO concentration in both patients and controls could imply overlooking small differences, which might have a pathogenetic importance.

In accordance with previous investigations we found a negative correlation between the urinary substance concentration of EGF/URO and increasing age [17]. This holds true also in childhood (Fig. 1). The same negative correlation was found when looking at the excretion of EGF/URO per mol creatinine (Table 1). The total daily output of EGF/URO was significantly smaller in the patients with interstistial cystitis and their controls as compared to the two other groups and their controls (Fig. 2). This difference can be explained by the age variation between the groups.

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