Changes in the Ratio of Urinary α1-Microglobulin to Ulinastatin Levels in Patients with Psychiatric Diseases

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Introduction

Alpha-1-Microglobulin (α1M, 31kDa) and ulinastatin* (UT, 40kDa) in human urine are derived from a similar precursor protein in the liver (Kaumeyer et al 1986). Hitherto, the physiologically relevant functions of these substances have not been clarified. The amino acid sequence of UT is not only highly homologous to the inhibitory domain of amyloid β-protein precursor associated with senile plaque or amyloid angiopathy (Kitaguti et al 1988; Ponte et al 1988; Tanzi et al 1988), but a UT-like immunoreactive substance with trypsin inhibitory activities is also found in brain sites related to memory and learning (Shikimi et al 1993). The relationships of urinary α1M and UT levels have been previously found to differ between the dementia and aged-matched control groups. In addition, different patterns of α1M/UT ratio in relation to the severity of dementia and duration of the disease have been displayed between Alzheimer-type senile dementia and vascular dementia patients (Inagaki et al 1995). In the present study, we studied further whether or not the relation between urinary levels of α1M and UT differed in patients with psychoses.

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* The generic name of this human urinary trypsin inhibitor has been recently changed from urinastatin to ulinastatin, as the substance is found not only in urine but also in serum.

Methods

Twelve patients with schizophrenia and 19 patients with mood disorder (10, patients with bipolar affective disorder; 9, patients with major depression) were diagnosed according to the DSM-Ⅲ-R (American Psychiatric Association 1987). Patients over 60 years of age were excluded in this study. The durations of schizophrenia and mood disorder in patients were 10.4 ± 2.3 and 6.1 ± 1.8 years (mean ± S.E.M), respectively. The respective severities of schizophrenia and mood disorder patients were 43 ± 6 (Brief Psychiatry Rating Scale, Overall and Gorham 1962) and 24 ± 4 points (Hamilton Depression Rating Scale, Hamilton 1960)(mean ±S.E.M). Patients with bipolar affective disorder (6 patients with and 4 without lithium treatment for at least 4 months) indicated neither manic nor depressive episodes for at least 30 days. All the patients with major depression were treated with antidepressants. As age-matched controls, 18 subjects without any present or past history of psychiatric diseases were included. None of the subjects indicated hepatic/renal dysfunctions or other malignant diseases. Informed consent was obtained from all subjects before the study.

Spontaneously collected urine (from the subjects) was centrifuged at 1,000 x g for 10 min at 4°C to remove debris and amorphous salts prior to storage at -50°C until assay. Urinary levels of α1M and UT were measured with ELISA, whereby galactosidase-labelled goat anti-rabbit IgG was interacted

(Biotrin International, Dublin) with rabbit anti-α1M IgG (Dako Co., Copenhagen) and rabbit anti-UT IgG (Shikimi et al 1990), respectively. Standard α1M (Dako Co., Copenhagen) and UT were used as references. Creatinine levels in the urine were measured with a photometric assay based on the Jaffe reaction (Wako creatinine kit, Wako Chemicals, Osaka). Urinary levels of α1M and UT were expressed as μg/mg creatinine to correct for the dilution rate of urine samples.

Linear regression analyses were evaluated by using the Stat View Ⅳ system (Abacus Concept, Inc., CA). Statistical significance was verified by the factorial ANOVA followed by Scheffe's post hoc test. Values where $p<0.05$ were considered statistically significant.

Results

In the bipolar affective disorder group, significant differences in the age and urinary levels of creatinine, α1M and UT, and α1M/UT ratio were not detected between the lithium-treated and untreated patients. The lithium-treated and untreated patients were thus pooled as a bipolar affective disorder group. In the Table 1, age and levels of creatinine, α1M and UT did not differ

significantly among the control, schizophrenia, mood disorder groups and its subdivided groups (bipolar affective disorder and major depression). The α1M/UT ratio of the mood disorder group, but not the schizophrenia group, was significantly higher than that of the controls ($P<0.01$). The bipolar affective disorder patients, but not the major depression cases, contributed to this change.

Relating urinary levels of UT and α1M, a positive correlation was observed in the control, schizophrenia and mood disorder groups, accordingly (Fig. 1). A similar tendency was manifested by the bipolar affective disorder and major depression groups (Fig. 2). Although the regression slope of the schizophrenia cases was not statistically different from that of controls, a significant difference was noted between the mood disorder and control groups ($P<0.05$). Between the schizophrenia and mood disorder groups, the regression slope was significantly ($P<0.05$) different. Furthermore, the regression slope of the major depression group, but not the bipolar affective disorder group, was statistically ($P<0.05$) different from those of controls and schizophrenia groups. In the schizophrenia and mood disorder groups, neither the scores from psychiatric rating scales (Brief Psychiatric Rating Scale and Hamilton Depression Rating Scale) nor durations of disease correlated well with the urinary levels of α1M or UT, or α1M/UT ratio.

Discussion

Comparing the schizophrenia and control groups, there were no significant differences in the regression slopes, urinary levels of α1M and UT, and α1M/UT ratio. Furthermore, neither the scores of Brief Psychiatric Rating Scale nor durations of the diseases correlated well with the urinary levels of α1M or UT. These findings suggest that the urinary levels of α1M and UT and α1M/UT ratio are not influenced by the pathophysiology of schizophrenia.

Comparing the mood disorder and control groups, the regression slope of the former differed from that of controls. Within the mood disorder category, the slope of the major depression group was especially significant ($P<0.05$). Furthermore, the α1M/UT ratio of mood disorder was significantly ($P<0.01$) higher than that of controls. Within the mood disorder category, the α1M/UT ratio of the bipolar affective disorder group was particularly significant ($P<0.01$). These results suggest that the relationships between the urinary levels of α1M and UT in mood disorder as a whole differ from those of controls.

Comparing the mood disorder category (and inclusive of bipolar affective disorder and major depression) with schizophrenia patients, the regression slopes of the mood disorder as a whole

and major depression groups differed from that of schizophrenia.

In our previous study (Inagaki et al 1995), a positive correlation between urinary levels of α1M and UT has been observed in dementia patients. The respective regression slopes of dementia groups (Alzheimer-type and vascular-type) were significantly different from that of non-demented controls in spite of insignificant difference in the α1M/UT ratio. Therefore, the relation between urinary levels of α1M and UT differed among the schizophrenia, mood disorder as a whole and dementia patients.

The α1M/UT ratio of bipolar affective disorder group was significantly higher than that of controls. However, lithium medication (60 % in the group were medicated with lithium) did not affect the change. This was advocated by insignificant differences in the urinary levels of creatinine, α1M and UT and α1M/UT ratio between lithium-treated and untreated patients. With regard to diet, variations in the urinary levels of α1M and UT and α1M/UT ratio were not observed. In addition, even in patients with urological diseases, the regression slope relating to urinary levels of α1M and UT remained statistically insignificant from that of healthy subjects (Shikimi et al 1994). However, the regression slope of the mood disorder group differed from that of controls. As none of the present subjects indicated

any renal dysfunctions, renal factors contributing to changes in the relation between urinary levels of α1M and UT in mood disorder patients may be discounted.

Glucocorticoid-responsive elements (Diarra-Mehrpour et al 1990) and interleukin 6 sequence motifs (Vetr and Gebhard 1990) have been found in a gene of the α1M- and UT-derived precursor protein. In addition, glucocorticoid-associated fluctuations of UT in urine, in which plasma levels of glucocorticoids are reportedly affected by cytokines (Spolsky et al 1987; Hermus and Sweep 1990), have been observed (Faarvang 1962). The urinary levels of α1M, UT and α1M/UT ratio are also influenced by the forms (free and complexed) of α1M and UT existing in plasma (α1M and UT complexes respectively exist in IgA-complexed (Demars et al 1989) and IgG-complexed forms (Hochstrasser et al 1981)), since only the free forms of these substances are found in urine (Jönsson-Berling et al 1989; Demars et al 1989). In the etiology of psychosocial diseases, the immune system has been focused as a key factor (Smith 1991). Changes in the systemic immune system, neuroimmune mechanisms in the central nervous system and/or cytokine concentrations at peripheral sites in psychoses may be associated with the variable relationships between urinary levels of α1M and UT. Although the exact mechanism(s) and physiological significance of the α1M/UT ratio warrant further studies, our

present findings suggest that a change in the relationship between urinary levels of α1M and UT reflects the psychoneurological differences underlying the various psychiatric diseases in human.

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Table 1. Number, sex, age, levels of creatinine, α1-microglobulin (α1M) and ulinastatin (UT), and α1M/UT ratio in urine of subjects

	Normal Control	Schizophrenia	Mood disorder		
			Bipolar	Depression	Total
Number of Subjects	18	12	10	9	19
Sex (M/F)	10/8	6/6	5/5	5/4	10/9
Age (years)	40 ± 2	34 ± 3	42 ± 3	33 ± 4	38 ± 3
Cr (mg/ml)	1.37 ± 0.16	0.97 ± 0.24	0.96 ± 0.17	1.37 ± 0.12	1.15 ± 0.11
α1M (μg/mg Cr)	6.87 ± 0.81	6.56 ± 0.83	9.77 ± 1.13	6.90 ± 1.21	8.41 ± 0.87
UT (μg/mg Cr)	10.34 ± 1.33	7.75 ± 1.39	6.76 ± 1.20	5.22 ± 0.77	6.03 ± 0.73
Ratio (α1M/UT)	0.75 ± 0.09	1.16 ± 0.21	1.65 ± 0.17[a)]	1.36 ± 0.15	1.51 ± 0.12[a)]

Values in age and urinary levels of creatinine (Cr), α1M, UT and α1M/UT ratio are represented as mean ± S.E.M.. Abbreviations: Bipolar, bipolar affective disorder; Depression, major depression. Superscript a) represents values (where $P<0.01$) significantly different from those of controls.

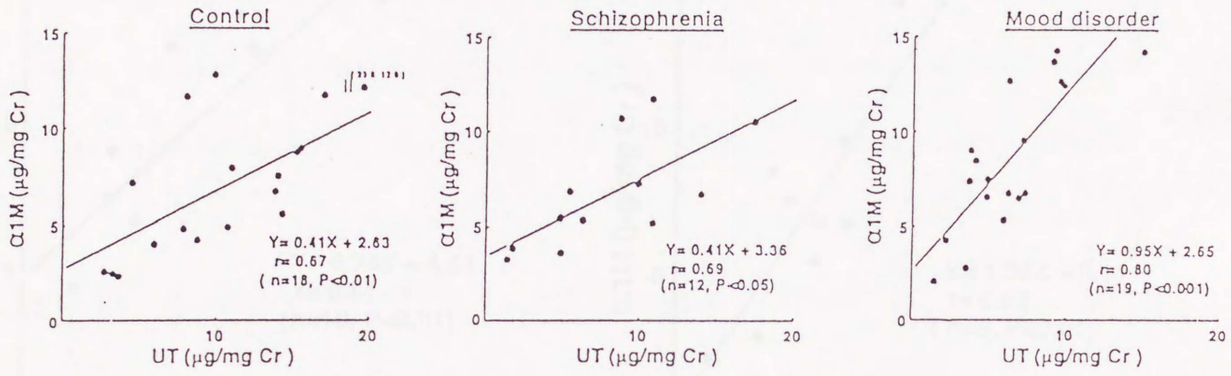

Fig.1. Correlation between urinary levels of ulinastatin (UT) and α1-microglobulin (α1M) in age-matched controls and patients with either schizophrenia or mood disorders. The correlation coefficient and number of subjects are represented with r and n in parentheses, respectively. Cr represents creatinine in urine.

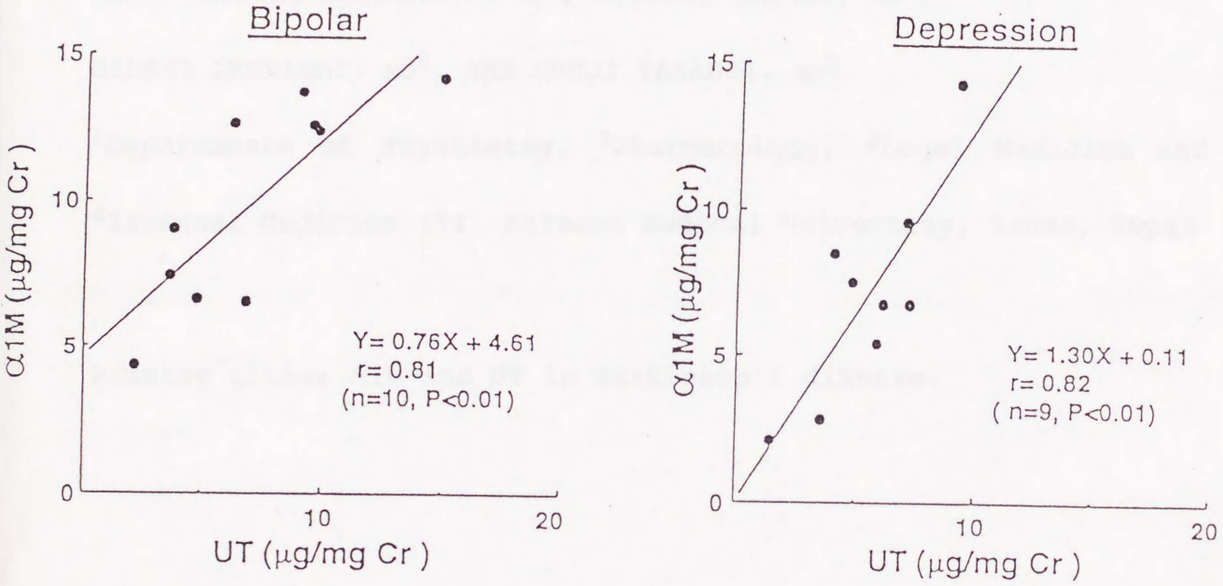

Fig.2. Correlation between urinary levels of ulinastatin (UT) and α1-microglobulin (α1M) in patients with bipolar affective disorder (Bipolar) or major depression (Depression). The correlation coefficient and number of subjects are represented with r and n in parentheses, respectively. Cr represents creatinine in urine.