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Eicosanoid and amino acid metabolism in transient acute psychoses with psychedelic symptoms

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Summary It has been hypothesized that a disturbance of glutathione (GSH) metabolism might be a common factor in many psychiatric disorders. The aim of the present study was to test this hypothesis in transient acute psychotic patients with distorted perceptions. Since the metabolism of GSH is related to that of thromboxane B_2 (TXB_2), prostaglandin E (PGE) and some amino acids, we determined these substances in the plasma of 15 patients and 17 normal controls. Plasma concentrations of TXB_2 were significantly higher and concentrations of serine and tryptophan were significantly lower in patients than in controls. Large variation was observed in plasma PGE levels in patients, although mean values did not differ significantly from controls. These results are consistent with the hypothesis that the metabolism of GSH is impaired in transient psychotic states.

INTRODUCTION

Eicosanoids are one of the many substances that have been implied in psychosis and schizophrenia.[1] An early hypothesis that schizophrenia may be a prostaglandin (PG) deficiency disease was based on the following facts: (a) many antipsychotics stimulate prolactin secretion, which in turn stimulates PG synthesis, (b) schizophrenia excludes pain, inflammation and rheumatoid arthritis and concomitant PG levels are low and (c) schizophrenia-like syndromes can be induced by PG antagonists.[2] However, the results of PG supplementation studies are contradictory[1] and plasma levels of PGE_2 in schizophrenic patients were found to be both decreased[3] and increased.[4] On the other hand, increased plasma phospholipase A_2 (PLA_2) activity has been found in schizophrenic patients and antipsychotic drugs like haloperidol, chlorpromazine and trifluoperazine, reduced the activity of PLA_2.[5] Since PLA_2 is a key enzyme in the formation of arachidonic acid from phospholipids, up-regulation of prostaglandin synthesis in schizophrenia is more likely and the clinical effect of antipsychotic drugs is not due to elevation of prolactin but rather a result of PLA_2 inhibition.

A special type of psychosis – the transient acute polymorphic psychosis with or without symptoms of schizophrenia according to ICD-10 criteria[6] – has been studied by Bruinvels et al[7] and Fekkes et al.[8] This psychosis is characterized by psychosensory symptoms of the type seen after LSD ingestion. From the available biochemical data it was hypothesized that the disturbed metabolism of serine (Ser) in these patients leads to an increased formation of N^5,N^{10}-methylene-tetrahydrofolate. The latter substance can dissociate into among others formaldehyde, which in turn may react with indolamines yielding β-carbolines, of which some are hallucinogenic.[7]

Studying the biochemistry of schizophrenic and the above mentioned psychotic patients, it became apparent

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that there is one factor in common with all described biochemical alterations, viz the metabolism of glutathione (GSH). Evidence that alterations in GSH metabolism may be involved in psychiatric manifestations comes from the observation that schizophrenic women exhibit abnormal activities of GSH peroxidase[9] and that schizophrenics may benefit from GSH infusion.[10] The hypothesized excess in formaldehyde levels in the transient psychotic patients may be explained by a combination of an increased Ser metabolism and a decreased formaldehyde dehydrogenase activity, due to a low level of its co-enzyme GSH.

In the present study, we examined the alterations in GSH in an indirect way in transient psychotic patients with psychedelic symptoms and normal controls by measuring the plasma levels of some amino acids related to GSH metabolism and the levels of PGE and thromboxane B_2 (TXB_2). The eicosanoids were measured, because the formation of PGE is dependent on the co-factor GSH[11] and TXB_2 levels have been found to be inversely correlated with GSH levels.[12]

SUBJECTS AND METHODS

Subjects

15 transient acute psychotic patients all with distorted sensory perceptions (8 female, 7 male; age = 34 ± 12 years, mean ± SD), who were drug-free for at least 3 weeks, and 17 normal controls (10 female, 7 male; age = 32 ± 6 years, mean ± SD), were included in the study. All patients were diagnosed according to ICD-10 criteria:[6] 9 patients suffered from polymorphic episodic psychosis (F 23.0 and 23.1), 4 from organic delusional schizophrenia-like disorder (F 06.2), 1 from mania with psychotic symptoms (F 30.2) and 1 from substance abuse disorder (cannabinoids; F 12.53). At the moment of blood sampling the mental states of the patients were rated as not psychotic ($n = 3$), slightly disturbed, e.g. depersonalization ($n = 4$) and full-blown psychotic ($n = 8$). From one polymorphic psychotic patient, in whom psychedelic symptoms could be evoked with Ser, a sample was taken during two different periods of full-blown psychosis. For statistical reasons biochemical determinations of these two samples were averaged.

The study was approved by the Medical Ethical Committee of the university.

Procedures

Venous blood samples were drawn between 09:00 and 10:00, using 10 ml siliconized monoject tubes containing 0.15% EDTA. Blood was centrifuged for 20 min at 20°C and 2650 × g_{max} and the plasma was stored at –30°C until analysis.

Laboratory methods

Amino acid analysis was performed as described previously.[13] We also determined the so-called TSM-ratio, which is defined as the ratio of 100 times the taurine (Tau) concentrations in plasma and the product of the plasma concentrations of Ser and methionine (Met).[8]

Determination of the eicosanoids PGE and TXB_2 was performed by a simple and routine radioimmunoassay.[14]

Statistics

Group differences were tested with a multivariate analysis of variance (MANOVA), followed by univariate analysis of variance (ANOVA) for each individual variable. Homogeneity of variance was tested using Box's M-test. The values given are means ± SD; the level of significance was set at 5% (two-tailed).

RESULTS

The plasma concentrations of the measured amino acids and eicosanoids are shown in Table 1. Ser, Met and PGE were not normally distributed. Therefore, a logarithmic transformation was performed on these variables for statistical analysis. Two cases were omitted due to the occurrence of extreme values. One case was the patient suffering from mania with psychotic symtoms, who exhibited an extremely high plasma level of TXB_2, viz 2432 pg/ml (normal value in this study: 173 pg/ml). Although the numerical value was not reliable, this patient was no exception in the way patients deviated from controls. The other case was a patient suffering from polymorphic psychosis, who showed a very low (18 pg/ml) plasma level of PGE (normal value in this study: 781 pg/ml). The multivariate test yielded statistically significant results ($F = 4.61$; df = 7.22; $P = 0.003$). Univariate F-tests showed that this effect could be attributed to differences in Ser, tryptophan (Trp), TXB_2 and the TSM-ratio (Table 1).

The plasma Ser and Trp levels of the psychotic patients

Table 1 Concentrations of amino acids, TXB_2 and PGE, and TSM-ratios in plasma of patients and normal controls.

Variable	Controls ($n = 17$)	Patients ($n = 13$)	*P* value
Tau (μmol/l)	52 ± 12	51 ± 11	NS
Ser (μmol/l)	136 ± 35	107 ± 21	0.012
Met (μmol/l)	26 ± 7	22 ± 3	NS
Trp (μmol/l)	50 ± 12	35 ± 12	0.003
TSM-ratio	1.69 ± 0.71	2.30 ± 0.62	0.020
TXB_2 (pg/ml)	173 ± 106	382 ± 122	< 0.001
PGE (pg/ml)	781 ± 185	862 ± 458	NS

All results are expressed as means ± SD. n = number of individuals. NS = not significantly different from controls.

were significantly lower than those of normal controls (ANOVA, $P = 0.012$ and 0.003, respectively; Table 1). Met levels were also lower, but these differences were not significant. Mean plasma Tau levels did not differ between the two groups. The TSM-ratio appeared to be higher in the patients than in the control group ($P = 0.020$). Of the eicosanoids, the TXB_2 levels in plasma of the patients were significantly higher than those of the controls ($P < 0.001$), whereas mean PGE levels did not differ between these groups. It has to be noted that the SD of the PGE levels in plasma of the patients was very high. Even in the same patient, variation in PGE levels were high. For instance, in the plasma of the patient of whom 2 blood samples were taken, the PGE levels were 0 and 1114 pg/ml, respectively.

Further subdivision of patients and controls regarding age, plasma levels of Tau, Ser, Met and Trp, the TSM-ratio, and the plasma levels of TXB_2 and PGE as measured variables against groupings of the subjects in patients and controls with subdivisions in male/female, mental state of the patient and other above mentioned characteristics, did not reveal any further significant differences.

DISCUSSION

The aim of this study was to find more solid proof for the hypothesis that in a group of psychiatric patients, suffering from transient acute psychotic disorders with psychosensory symptoms, GSH metabolism is altered. Indirect measurement of GSH by way of determination of the plasma levels of the eicosanoids TXB_2 and PGE was chosen, because we lack the technique to measure GSH. The two parameters TXB2 and PGE were selected, because TXB_2 concentrations have been found to be inversely correlated with GSH concentrations[12,15,16] and PGE uses GSH as a co-substrate for its formation.[11,16]

As explained above, the patients suffering from polymorphic psychosis are expected to have increased formaldehyde levels.[7] Whether this is due to a deficiency in GSH synthesis or that excess formaldehyde leads to a reduction in GSH concentration is not clear. In any case, our finding of a two-fold increase in TXB_2 in all patients versus controls (Table 1) is in line with a decreased GSH availability. Although the mean plasma PGE levels did not differ between the two groups, its variation in the patient group was 2.5 times higher (SD = 494 pg/ml) than in the normal controls (SD = 185 pg/ml). This indicates that GSH concentrations in episodic psychotic patients may fluctuate rapidly. The patient observed during different periods of psychosis showed during both periods elevated plasma TXB_2 levels (708 and 610 pg/ml TXB_2, respectively), whereas the plasma PGE concentration was at one time elevated and at the other reduced (1114 and 0 pg/ml PGE, respectively). Probably, the determination of TXB_2 tells us more about the direction of change in GSH levels than the measurement of PGE, because the effects of GSH on PGE are somewhat difficult to interpret. For instance, it has been found that formation of PGE_2 is inhibited in the presence of 1 mM GSH, whereas 0.1 mM GSH stimulated its synthesis.[17] Therefore, TXB_2 is regarded as the most important parameter.

A significant decrease in plasma Trp levels was found in the studied psychotic patients. This may be explained by an increase in the synthesis of NADPH – Trp is a precursor of NADPH – in order to keep sufficient GSH in a reduced state. It is conceivable that not only the absolute level of GSH is important, but also the ratio between reduced and oxidized GSH.

The observed increased TSM-ratio in the psychotic patients compared to normal controls is mainly due to a decrease in plasma Ser level, because the levels of Tau and Met were not changed significantly. The plasma Ser levels of the 9 patients suffering from polymorphic psychosis (ICD-10 categories F 23.0 and 23.1) were slightly lower than those of the whole patient group (98 ± 21 and 106 ± 20 μmol/l, respectively), while the TXB_2 levels were comparable (399 ± 145 and 373 ± 122 pg/ml, respectively).

In conclusion, the plasma TXB_2 levels of psychotic patients with distorted perceptions were found to be significantly higher than those of normal controls, while the concentrations of the amino acids Trp and Ser were lower. Moreover, the variation in plasma PGE levels of the psychotic patients was more than 2-fold higher than in the control group. All differences found point to a disturbance in the metabolism of GSH in transient acute psychosis and suggest that GSH is involved in the etiology of the psychosensory symptoms. Whether this must be interpreted in terms of active oxygen species involvement or excess formaldehyde formation cannot be answered yet.

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