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Low CSF Concentrations of Cyclic GMP in Schizophrenia

W. F. GATTAZ, H. CRAMER and H. BECKMANN

Summary: Increasing evidence suggests that the concentrations of cyclic guanosine 3′5′-monophosphate (cGMP) in the cerebrospinal fluid (CSF) may reflect central cholinergic activity. When the concentrations of this nucleotide in the CSF from 28 schizophrenic patients (13 without and 15 with neuroleptic treatment) and 16 psychiatrically healthy controls was determined the schizophrenics showed significantly lower CSF levels of cGMP as compared to controls.

As dopamine and homovanillic acid concentrations were not altered in these CSF samples, this finding of reduced cGMP suggests a cholinergic-dopaminergic imbalance in schizophrenia, with a reduction of the former and consequently a *relative* dominance of the latter.

The dopamine (DA)-hypothesis of schizophrenia is based upon the facts that (a) virtually all anti-psychotic drugs have a DA-receptor blocking effect and (b) that DA-agonists, i.e. amphetamine, are likely to produce a schizophrenia-like psychosis in certain individuals. However, studies on the concentrations of DA (Gattaz *et al,* 1982) and its metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) (Post and Goodwin, 1978; Gattaz *et al,* 1982a) have failed to provide a direct support for the assumption of an increased DA turnover in drug-free schizophrenics.

An accumulating body of evidence suggests that neuronal activity in the brain is controlled by a regulatory loop containing different transmitter systems (Fonnum *et al*, 1974; McGeer *et al*, 1973). Thus it seems reasonable to investigate other related systems in schizophrenia in an attempt to clarify the pathogenesis of this disease.

A functional interrelationship between the dopaminergic and the cholinergic systems has been postulated (Barbeau, 1962), mainly on the fact that anti-cholinergic drugs may improve some symptoms of Parkinson's disease.

The short half-life of acetylcholine (ACh) in body fluid makes it difficult to measure the concentrations of this transmitter in the CSF. A way out of this difficulty is to determine the CSF concentrations of cyclic guanosine 3′5′-monophosphate (cGMP), which has been shown possibly to reflect central cholinergic activity (Ebstein *et al*, 1976; Smith *et al,* 1976; Schindler *et al,* 1981).

Patients and Methods

This study is part of a larger biological investigation on this sample, which has already been described elsewhere (Beckmann *et al,* 1982; Gattaz *et al,* 1982).

The study comprises 28 paranoid schizophrenic patients (all males, caucasian, mean age 30.6±8.0 years) consecutively admitted at the Clínica Borda do Campo (Sao Paulo, Brazil) and 15 controls (13 males and 2 females, mean age 35.0±15.7 years). Since the results obtained in these two females were very similar to those in males, data were considered together.

Patients were diagnosed according to the Research Diagnostic Criteria (Spitzer *et al,* 1975). Two experienced psychiatrists evaluated independently their psychopathological state by means of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Fifteen patients were under treatment with neuroleptic drugs (butyrophenones and phenothiazines) for at least 3 weeks (mean dose ± SD in chlorpromazine-equivalents = 585±755 mg/day). Thirteen patients did not take any drug for a period of at least 4 weeks prior to the study.

As expected, patients under neuroleptic therapy had significantly lower Activation scores on the BPRS than patients without neuroleptics ($P < 0.05$). No other significant difference was found in the psychopathological scores between the two groups (age 31.8±10.1 and 29.3±4.4 years; age at onset 20.6±5.4 and 21.8±3.8 years; duration of disease 10.8±6.8 and 8.3±4.5; number of hospitalisations 13.6±10.0 and 7.6±7.3).

Controls were subject with nonspecific neurological symptoms (headaches, dizziness, etc.) which necessitated a lumbar puncture for diagnostic reasons and were not under drug treatment at this time.

Informed consent was obtained from all of the

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subjects or their first degree relatives after the nature of the study and its possible complications have been fully explained.

CSF was obtained by lumbar puncture in a sitting position between 9 and 10 a.m., after probands had fasted for 12 hours and had a bed rest for 10 hours. Sixteen ml of CSF were removed without additions. To avoid rostral-caudal gradient effects, samples were gently mixed and then immediately frozen on dry ice and stored in a freezer at −50°C. When the clinical work was concluded, samples were transported from Brazil to Germany on dry ice and then stored at −70°C until analyzed.

The CSF concentrations of cGMP were determined by radioimmunoassay as described by Cailla *et al* (1976). The biological determinations were carried out blind. Non-parametric tests (Mann-Whitney U-test and Spearman correlation coefficients) were used for the evaluation of the data.

Results

Results are summarized in the Fig. The CSF concentrations of cGMP were significantly lower in the subgroup of schizophrenic patients *without* neuroleptics as compared to controls (2.62±0.88 vs. 3.97±1.24 pMol/ml, P <0.005). In the group of patients under neuroleptic therapy this difference was just below the level of significance (2.83±1.21 pMol/ml, P = 0.04). There was a significant correlation between CSF levels of cGMP and the number of psychiatric hospital admissions (r_s = .48, n = 27, P <0.005).

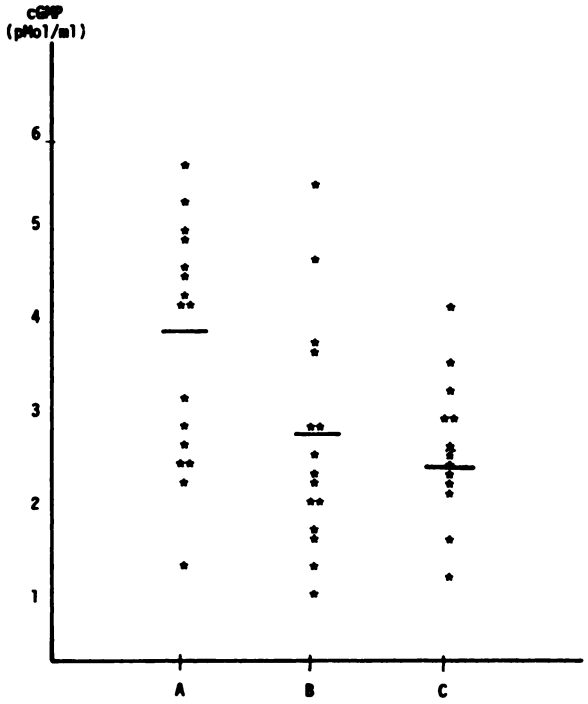

FIG.—CSF concentrations of cGMP (in pMol/ml) in controls (A), patients with neuroleptics (B) and patients without neuroleptics (C).

No correlations were found between the CSF concentrations of cGMP and the psychopathological scores of the BPRS or other variables.

Discussion

The mean CSF concentrations of cGMP in our sample are similar to those reported in two other studies (Ebstein *et al*, 1976; Smith *et al*, 1976) which have found a tendency toward lower levels of the nucleotide in schizophrenic patients. Furthermore, the somewhat increased levels of cGMP in patients under neuroleptic therapy in the present study have been clearly observed by Ebstein *et al* (1976), who have reported an increase by 50 per cent in the mean CSF levels of cGMP after two months treatment with phenothiazines. A similar increase has been observed by Zimmer *et al* (1980) in a group of schizophrenic patients after 30 days treatment with sulpiride. In this regard the correlation in the present study between CSF levels of cGMP and the number of psychiatric hospital admissions is interesting as the latter might assess indirectly the amount of drug intake through the course of the disease.

As stated above, experimental evidences suggest that the CSF concentrations of cGMP reflect to a considerable extent the central cholinergic activity. This is supported by the recent report of Schindler *et al* (1981) of a dose-dependent increase in the CSF accumulation of the nucleotide after the administration of carbamylcholine, a cholinergic agonist.

In face of these facts, the findings of reduced cGMP in schizophrenics could suggest a reduced cholinergic activity in those patients. It is unlikely that this reduction would reflect a disturbed relationship between cGMP and calcium in our sample (Schindler *et al*, 1981), as no differences were found in the calcium concentrations between patients with and without neuroleptics and controls (Gattaz and Beckmann, unpublished results).

Ebstein *et al* (1976), taking into account the probable inhibitory effect of DA on post-synaptic cholinergic neurons, suggested that an increased release of DA in schizophrenia could be responsible for the reduced cholinergic activity. However, as reported elsewhere (Gattaz *et al*, 1982 and 1982a), we could not observe *in the present sample* an indication of increased DA release, as the CSF concentrations of both DA and its major metabolite homovanillic acid in

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the patients *without* neuroleptics were not different from those in healthy controls. Therefore, an increased DA release is unlikely to account for the lower cGMP levels in our drug-free patients.

Several studies have pointed to a functional balance between the cholinergic and the dopaminergic systems in the brain (Anden and Bedard, 1971; Bartholini *et al*, 1973; Guyenet *et al*, 1975; Ladinsky *et al*, 1975). Thus, even in face of a normal dopaminergic function in schizophrenia, a reduced cholinergic activity would result in a *relative* hyperfunction of the dopaminergic system. We speculate whether this cholinergic-dopaminergic imbalance could be viewed as one possible factor underlying the etiology of the disease. In this context, the tendency shown by neuroleptics to increase cGMP concentrations could be understood as a restoration of the cholinergic-dopaminergic balance (Ebstein *et al*, 1976) through cholinergic stimulation and dopaminergic blockade. This assumption is in line with laboratory experiments which showed an increased ACh release in the CNS after the administration of neuroleptics (Stadtler *et al*, 1973; Trabucchi *et al*, 1974). Interestingly, amphetamines, which can produce a schizophrenia-like psychosis, have been found to work in the opposite direction, namely reducing markedly the ACh turnover in the brain (Trabucchi *et al*, 1975).

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