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Monoamine Metabolite Levels in Cerebrospinal Fluid of Psychotic Women Treated with Melperone or Thiothixene*

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Summary. Psychotic women with schizophrenic symptoms were treated with melperone 100 mg × 3 ($n = 29$) or thiothixene 10 mg × 3 ($n = 34$) using a double-blind procedure. Before and during treatment, levels of HVA, MOPEG, and 5-HIAA, the major metabolites of DA, NE, and 5-HT, were determined in lumbar cerebrospinal fluid by a mass fragmentographic technique. Both treatments resulted in an elevation of the HVA levels after 2 weeks, thiothixene having a more marked effect. The effect of thiothixene but not of melperone persisted after 4 weeks. Thiothixene did not influence the MOPEG level, but melperone reduced it after 4 weeks of treatment. The 5-HIAA levels were not significantly altered by the drugs. The HVA/MOPEG and the HVA/5-HIAA ratios were highly significantly elevated by both drugs after 2 as well as 4 weeks. Thiothixene induced a significantly greater change of these ratios than melperone. The results supply evidence that thiothixene accelerates central dopamine metabolism in man, presumably by blocking DA receptors. Melperone appears to act similarly, but has an effect which is weaker and/or of shorter duration. During long-term treatment with melperone the receptors develop tolerance to it. The acceleration in DA metabolism declines and the effect of melperone switches instead to central NA metabolism. The results indicate that both drugs cause long-term changes in the activity ratios of central monoamine systems. It is suggested that such changes in several systems rather than single biochemical events may be related to the antipsychotic effects of neuroleptic drugs. This study also demonstrated the versatility of using monoamine metabolite analysis of the CSF as a tool for the quantification of biochemical effects of neuroleptic drugs on the human CNS.

Key words: Cerebrospinal fluid – Neuroleptics – Melperone – Thiothixene – Homovanillic acid – 5-Hydroxyindoleacetic acid – 4-Hydroxy-3-methoxyphenylethylene glycol – Schizophrenia.

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Introduction

There is extensive evidence that antipsychotic drugs with different chemical structures accelerate dopamine (DA) metabolism in the brain of experimental animals (Carlsson and Lindqvist, 1963; for review see Sedvall, 1975). Some of the antipsychotics also accelerate the metabolism of brain norepinephrine (NE) (Carlsson and Lindqvist, 1963; Andén et al., 1970). These effects are generally assumed to result from the activation of feedback mechanisms from central receptors blocked by the drugs (Carlsson and Lindqvist, 1963).

Earlier evidence of the effects of neuroleptics on brain DA metabolism in humans was ambiguous (Persson and Roos, 1968; Bowers et al., 1969; Sjöström and Roos, 1972). However, recent studies, using mass fragmentography, demonstrated a marked elevation of the homovanillic acid (HVA) concentration in cerebrospinal fluid (CSF) of patients treated with chlorpromazine or other types of antipsychotic drugs (Fyrö et al., 1974; Sedvall et al., 1974; Post and Goodwin, 1975; Sedvall et al., 1975).

Thiothixene, a thioxanthene derivative, and melperone, a butyrophenone derivative, have been said to exert antipsychotic effects in schizophrenic patients (Schulsinger et al., 1965; Bishop et al., 1966; Gallant et al., 1966; Gross and Haberler, 1970; Jacobsson et al., 1976). Both drugs have also been shown to exhibit neuroleptic effects in animal behavioral tests (Christensen et al., 1965; Weissman, 1974) and markedly to elevate levels of the major DA metabolite in the brain of mice and rats (Sedvall et al., 1976; Wiesel et al., 1977).

The DA, NE and 5-hydroxytryptamine (5-HT) systems constitute three major central monoaminergic transmitter pathways in the brain. Recently a highly sensitive and specific mass fragmentographic method was developed for the simultaneous determination in CSF of the major metabolites of these systems, i.e., HVA, 4-hydroxy-3-methoxyphenylethylene glycol (MOPEG) and 5-hydroxyindoleacetic acid (5-HIAA) (Swahn et al., 1976). The aim of the present study was to investigate whether thiothixene and melperone in therapeutic doses affect monoamine metabolism in the central nervous system of psychotic patients. The levels of HVA, MOPEG, and 5-HIAA were measured by mass fragmentography in lumbar CSF of psychotic women before and during drug treatment.

Material and Methods

The protocol of the present investigation which aimed at studying the relations between clinical and biochemical effects in drug-treated psychotic patients was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden. The present paper concerns the effect of the drugs on the monoamine metabolites in CSF. The therapeutic effects are reported elsewhere (Bjerkenstedt et al., 1977). All the patients gave their consent to participate in the study. A total of 81 acutely admitted psychotic women were selected from the emergency ward according to the following criteria:

Criteria for Inclusion. Presence of thought disorder, delusions or auditory hallucinations.

Criteria for Exclusion. Organic brain disease, somatic disease, toxicomania, manic or depressive psychoses, and symptoms of borderline personality. Another criterion was that the patients had not been treated with an antipsychotic drug during the month preceeding admittance. This

criterion was fulfilled for 43 patients. Eighteen patients were excluded from the study because of refusal to take the drug, refusal of lumbar puncture, side effects or other intercurrent causes. Of the remaining 63 patients, 20 (thiothixene: 9, melperone: 11) had received single doses of various types of antipsychotic drugs during the preceeding month but not within the last 48 h before the first lumbar puncture. Since the data from these patients did not differ significantly from those of the untreated group, the data from both groups of patients were pooled. The average age was 38, ranging between 19 and 63 years, and the age distribution did not differ significantly for the two groups.

Administration of Drugs. During an initial period lasting from 1 to 21 days, placebo tablets were administered. During this interval blood and CSF samples were taken and the clinical condition was rated by a procedure described in Bjerkenstedt et al. (1978). After the placebo period, thiothixene tablets (Navane, Roerig, Sweden, 10 mg) or melperone tablets (Buronil, Ferrosan, Sweden, 100 mg) were administered using a double-blind procedure. Thiothixene was given to 34 patients and melperone to 29. The double-dummy technique was used, i.e., one group of patients received tablets containing thiothixene plus placebo tablets having an appearance identical to those containing melperone. The other group received melperone tablets plus placebo tablets that were identical to those containing thiothixene. During the first week one placebo tablet and one tablet of active compound were given at 0800 h and at 1600 h. After the first week the dose was increased to three tablets per day of the active compound as well as the placebo, the additional tablets given at 1200 h. During the remaining part of the study this dose was kept constant. CSF samples were taken again after 2 and 4 weeks of active drug treatment. Twenty-one patients (thiothixene: 12, melperone: 9) received occasional doses of diazepam (Stesolid, Dumex AB, Sweden) for sleep induction (5—10 mg) and sedation (5—10 mg × 4) during the study. All these 21 patients were also occasionally prescribed diazepam during active neuroleptic treatment, while 5 patients also received it during the placebo period. Fifteen patients (thiothixene: 11, melperone: 4) also received biperiden (Akineton, AB Meda, Sweden, 5 mg × 3). Severe extrapyramidal symptoms motivated the administration of biperiden. In order to eliminate the disturbing effects of biperiden and diazepam these effects together with treatment groups, were included in a general analysis on a variance model. With one exception the data from the patients treated with diazepam and biperiden were not significantly different from those who received only the experimental drugs (see further: Results, D).

Sampling of CSF. The samples of lumbar CSF were taken at 0800 h. All patients had been fasting for 12 h before the puncture, which was performed before the patient left his bed and before the administration of the first drug dose of the day. A sample of about 12.5 ml of CSF was taken with the patient in a sitting position. After being mixed, the sample was divided into 2 ml portions and stored at below —20° C pending analysis. Storage of CSF samples for 6 months does not result in any significant diminution of the monoamine metabolite levels. The contents of HVA, MOPEG and 5-HIAA were determined according to the procedure described by Swahn et al. (1976). The analysis, using double samples, was usually performed within 2 months after the puncture. The CSF from the three different punctures of each patient were analyzed on the same day.

Statistical calculation of differences of means from paired and unpaired data, correlation coefficients, t-tests, and analysis of variance were computed by conventional statistical methods (Overall and Klett, 1972; Snedecor and Cochran, 1967). All tests were two-sided.

Results

A. Pre-Treatment Levels of HVA, MOPEG and 5-HIAA in CSF of Psychotic Women

The levels of HVA, MOPEG and 5-HIAA of the psychotic women before treatment (Figs. 1—3) were of the same order as those previously reported (Chase et al., 1970; Gottfries et al., 1971; Shopsin et al., 1973; Sjöström and Roos, 1972;

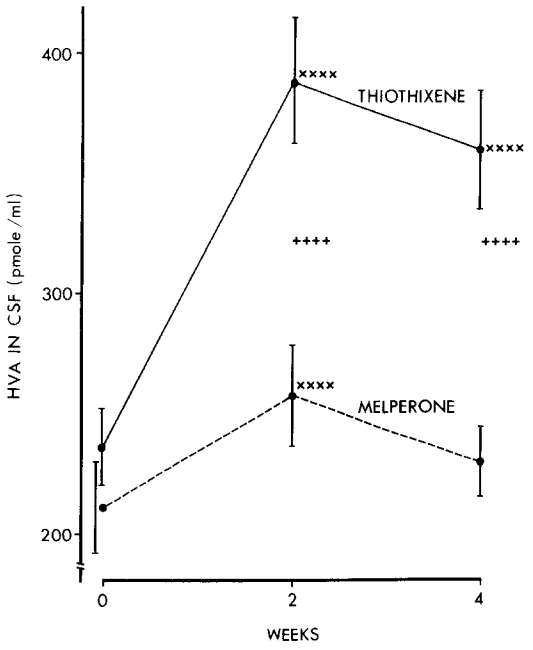

Fig. 1. Levels of HVA in CSF of psychotic women before and during treatment with melperone or thiothixene. Each point refers to mean ±SE.++++ $P<0.001$ difference between treatment groups. ×××× $P<0.001$ difference compared to pretreatment level. ××× $P<0.01$. ×× $P<0.02$. × $P<0.05$

Fyrö et al., 1974). The metabolite levels before treatment did not differ significantly in the melperone and the thiothixene groups.

B. The Effects of Melperone or Thiothixene on the HVA Levels in CSF of Psychotic Women

In the melperone-treated patients the HVA level was elevated only after 2 weeks ($P<0.001$). Between 2 and 4 weeks a reduction of the HVA level ($P<0.025$) occurred in this group (Fig. 1).

In the thiothixene-treated patients the HVA level was elevated ($P<0.001$) after 2 as well as 4 weeks (Fig. 1). The levels did not differ significantly at 2 and 4 weeks. At 2 as well as 4 weeks of treatment the HVA levels were higher ($P<0.001$) in the thiothixene-treated patients, compared to those who received melperone.

C. The Effects of Melperone or Thiothixene on MOPEG Levels in CSF of Psychotic Women

The MOPEG level did not change during the first 2 weeks of melperone treatment (Fig. 2); but after 4 weeks MOPEG was significantly reduced in comparison to the pretreatment and the 2-week levels ($P<0.001$; $P<0.02$). After 4 weeks the MOPEG level in the melperone-treated patients was also significantly lower than that of the thiothixene-treated patients. Thiothixene treatment did not alter the MOPEG level in CSF.

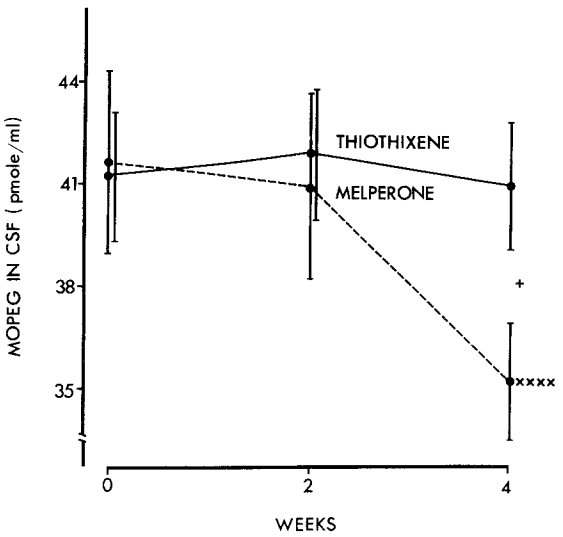

Fig. 2. Levels of MOPEG in CSF of psychotic women before and during treatment with melperone or thiothixene

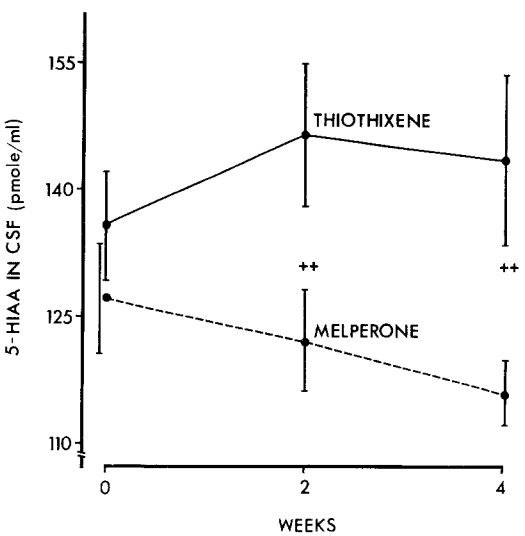

Fig. 3. Levels of 5-HIAA in CSF of psychotic women before and during treatment with melperone or thiothixene

D. The Effects of Melperone or Thiothixene on 5-HIAA Levels in CSF of Psychotic Women

Neither melperone nor thiothixene treatment altered the 5-HIAA levels significantly (Fig. 3); but the levels tended to increase in the thiothixene group, and they showed a tendency to decline during melperone treatment. This resulted in a lower 5-HIAA level ($P<0.025$) during melperone treatment than during thiothixene treatment when measurements were taken at 2 and 4 weeks.

Within each treatment group patients receiving diazepam tended to have lower levels of 5-HIAA. In the melperone group this effect was significant ($P<0.05$) at both 2 and 4 weeks. This was the only interaction observed between

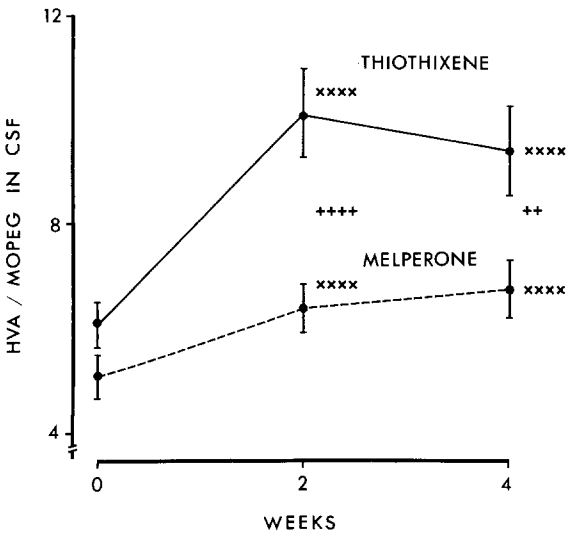

Fig. 4. The HVA/MOPEG ratio in CSF of psychotic women before and during treatment with melperone or thiothixene

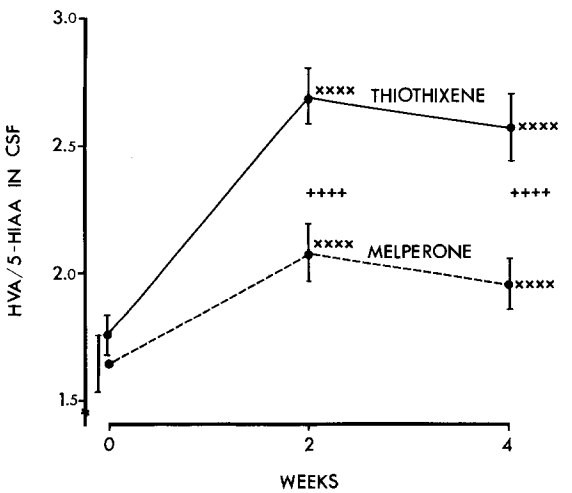

Fig. 5. The HVA/5-HIAA ratio in CSF of psychotic women before and during treatment with melperone or thiothixene

type of neuroleptics, diazepam, and monoamine metabolite level. However, when the diazepam-treated patients were excluded there was still a significant difference in the 5-HIAA levels in the melperone- and the thiothixene-treated patients.

E. The Effects of Melperone or Thiothixene on the HVA/MOPEG Ratio

Treatment with thiothixene as well as melperone resulted in elevated HVA/MOPEG ratios after 2 ($P<0.001$) as well as 4 ($P<0.001$) weeks (Fig. 4). Thiothixene treatment produced a significantly greater change in this ratio than melperone treatment.

Before treatment there was a tendency to a low, positive correlation between the levels of HVA and MOPEG in CSF ($r=0.36$, $P<0.01$).

Significant positive correlations between the levels of HVA and MOPEG at 2 and 4 weeks ($r = 0.71$, $P < 0.001$; $r = 0.34$, $P < 0.05$) were also found in the melperone group but not in the thiothixene group.

F. The Effect of Melperone or Thiothixene on the HVA/5-HIAA Ratio

Treatment with thiothixene as well as melperone elevated significantly the HVA/5-HIAA ratio at 2 as well as 4 weeks (Fig. 5); but thiothixene treatment produced a greater change than melperone treatment for this ratio also.

Before treatment the HVA level was significantly correlated to the 5-HIAA level ($r=0.68$, $P<0.001$).

In both the melperone- and the thiothixene-treated groups, correlations were also found between the levels of HVA and 5-HIAA after 2 as well as 4 weeks (melperone, $r=0.74$, $P<0.001$ and $r=0.66$, $P<0.001$; thiothixene, $r=0.75$, $P<0.001$ and $r=0.84$, $P<0.001$).

G. The Effect of Melperone or Thiothixene on the 5-HIAA/MOPEG Ratio

Neither melperone nor thiothixene altered the 5-HIAA/MOPEG ratio significantly.

In the melperone-treated patients a correlation was found between the levels of MOPEG and 5-HIAA ($r=0.58$, $P<0.001$) at 2 weeks.

Discussion

In accordance with results obtained using other antipsychotic drugs (Fyrö et al., 1974; Sedvall et al., 1974; Wode-Helgodt et al., 1977), treatment of psychotic patients with thiothixene or melperone induced significant changes in the monoamine metabolite levels in the lumbar CSF. Quantitative as well as qualitative differences between the drugs examined were obtained in this regard.

Similar to other neuroleptic drugs, thiothixene and melperone significantly elevated the level of the DA metabolite HVA. At the fixed doses used, which were selected to induce antipsychotic effects, thiothixene induced a change which was singificantly greater, 16 h after the last dose, than that induced by melperone. For both drugs the average elevation was highest after 2 weeks of treatment. In the thiothixene group there was a tendency towards tolerance and in the melperone group the tolerance was almost complete after 4 weeks. The HVA content in lumbar CSF has been shown to derive almost exclusively from the brain (Curzon et al., 1971; Post et al., 1973; Young et al., 1973; Gordon et al., 1975). The results are therefore compatible with the view that both thiothixene and melperone accelerate DA turnover and metabolism in the human brain and that thiothixene is more potent and/or longer-acting than melperone in this regard. The effects observed are in all probability related to a blockade of central DA receptors by the drugs. The mean values indicate the development of tolerance to the effects of both drugs on DA metabolism after 4 weeks of treatment. A similar attenuation was recently found for the HVA elevation in CSF of haloperidol- and chlorpromazine-treated patients (Post and Goodwin, 1975; Wode-Helgodt et al.,

1977). But only with melperone does the effect totally disappear after 4 weeks. The melperone levels in serum were higher (nonsignificantly) at 4 than at 2 weeks (Bjerkenstedt, 1978). Thus the mechanism for tolerance is in all probability predominantly due to pharmacodynamic events, possibly the development of hypersensitive DA receptors (Møller-Nielsen et al., 1976).

In the melperone group the MOPEG level was significantly reduced after 4 weeks. At this time interval, the MOPEG level was also significantly lower in the melperone-treated patients than in those receiving thiothixene. The difference indicates a qualitative difference between the effects of the two drugs. It is unlikely that the effect is due to increased transport of MOPEG from the CSF after melperone treatment. Thus treatment with melperone but not thiothixene seemed to result in a reduced NE metabolism. The slow appearance of the effect may indicate that it is dependent on a secondary alteration of metabolic events, possibly the induction of protein synthesis. In a similar study it was found recently that during chlorpromazine treatment of psychotic patients there was also a pronounced reduction of the MOPEG level in CSF (Sedvall et al., 1975; Wode-Helgodt et al., 1977). Treatment with nortriptyline has also been shown to reduce the MOPEG level in CSF (Bertilsson et al., 1974). The effects of chlorpromazine and nortriptyline appeared within a few weeks and may be related to the inhibition of NE reuptake (Hertting et al., 1961), which has been shown to result in reduced NE synthesis and turnover in the central nervous system (Nybäck et al., 1970). Such an inhibition of NE reuptake has not been demonstrated with melperone and appears less likely since butyrophenones are weak inhibitors of NE reuptake (Ross and Renyi, 1966). Contrary to the effect in the CSF of humans, in rat experiments acute administration of chlorpromazine or melperone in fairly high doses elevated MOPEG levels in the brain (Keller et al., 1973; Alfredsson et al., 1976; Wiesel et al., 1978), possibly indicating NE receptor blockade. The difference between the results of the human and animal experiments is unclear, but may be due partly to the fact that the MOPEG level in lumbar CSF reflects NE metabolism in the spinal cord (Post et al., 1973) whereas the MOPEG level in the brain is derived from different NE systems. The mechanism for the MOPEG reduction found here and the apparent species difference must be explored further.

The fact that the 5-HIAA level was not significantly altered by any of the drugs argues against the view that a nonspecific transport blockade caused the marked elevation of the HVA level. This lack of significant effect is also consistent with the results found in animal experiments (Sedvall et al., 1974; Wiesel et al., 1977). However, after treatment for 2 as well as 4 weeks the 5-HIAA level in CSF was significantly lower in patients treated with melperone than in those given thiothixene. Interestingly, the same result was found in mice treated with the two drugs (Sedvall et al., 1974). This result may suggest that there are also small but consistent effects of one or both drugs on the 5-HT system.

Since treatment of psychotic patients with melperone (Figs. 1 and 2) and chlorpromazine (Wode-Helgodt et al., 1977) was shown to alter the CSF levels of HVA as well as MOPEG, but in opposite directions, the ratio between the HVA and MOPEG levels was calculated. The calculation of the HVA/MOPEG as well as the HVA/5-HIAA ratios may be valid also for other reasons. Thus, the DA-

containing cell bodies in the midbrain have been shown to receive a noradrenergic and possibly also a 5-hydroxytryptaminergic innervation (Fuxe, 1965; Dray et al., 1976). Moreover, in several instances the levels of the metabolites in CSF were correlated to each other before as well as during treatment. This supplies morphologic and clinical evidence for interactions between the monoaminergic systems. The calculated HVA/MOPEG and HVA/5-HIAA ratios, which may possibly reflect the activity relations between the different monoamine systems, were highly significantly elevated by both drugs, but thiothixene induced a significantly greater change also in these constructed biochemical parameters. The data are consistent with the view that both drugs markedly affect the activity balance between the DA and the NE or 5-HT systems. It seems possible that changes in activity ratios of several systems rather than single biochemical events may be related to the antipsychotic effects of thiothixene and melperone.

The HVA level during melperone treatment declined between the second and fourth weeks simultaneously with the MOPEG level. This might indicate that the two phenomena are interrelated. This was in fact the case, since a highly significant correlation ($r=0.68$, $P<0.001$) was found between the changes in the two metabolites from week 2 to week 4, moreover the levels of the two metabolites were correlated after 2 as well as 4 weeks of treatment. It may be postulated that the induction of the MOPEG change by melperone counteracts the acceleration of impulse activity in DA neurons resulting in a smaller effect on the HVA level. Melperone may thus impair DA transmission by two mechanisms: by a fairly weak initial blockade of postsynaptic DA receptors and by an effect on the NE system which may result in a reduction of the impulse flow in the DA neurons. The combination of the two mechanisms may result in a marked inhibition of dopaminergic transmission which would explain the relatively slight elevation of the HVA level and possibly also the potent antipsychotic effect of melperone treatment (Bjerkenstedt et al., 1978). Thiothixene, on the other hand, appears to have no effect on the NE system and may impair dopaminergic transmission predominantly by blockade of postsynaptic DA receptors. Here the uninhibited feedback mechanisms would cause the marked acceleration of DA metabolism. Therefore the quantitative and qualitative differences between the biochemical effects of thiothixene and melperone do not exclude the possibility that they are mediating their antipsychotic effects by a similar mechanism, i.e., by impairment of dopaminergic transmission. However, it must also be taken into consideration that the slowly developing effect of melperone on the MOPEG level is of importance for its antipsychotic effect.

The present study has thus demonstrated the versatility of using monoamine metabolite analysis of the CSF as a tool for the quantitation of biochemical effects of neuroleptic drugs on the human CNS. The relations between the biochemical effects observed and the antipsychotic effects of the drugs merit further investigation.

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