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Effects of Melperone and Thiothixene on Prolactin Levels in Cerebrospinal Fluid and Plasma of Psychotic Women

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Summary. Levels of prolactin (PRL) were determined by radioimmunoassay in cerebrospinal fluid (CSF) and plasma from psychotic women before and during treatment with melperone 100 mg × 3 (n = 29) or thiothixene 10 mg × 3 (n = 34). Small amounts of PRL were found in the CSF of most patients before treatment. The level of PRL in CSF was about 20% of that in the plasma. Both drugs elevated PRL levels in CSF and plasma significantly. Thiothixene was more potent and also more long acting than melperone in this regard. For neither drug was there any marked tolerance to the effects within a 4 week period. The highest PRL level in CSF, 26 ng/ml, was found in a thiothixene treated patient.

Positive correlations were found between the contents of PRL in CSF and plasma before treatment. During thiothixene treatment there were also significant positive correlations between PRL levels in CSF and plasma. During melperone treatment this correlation was probably significant only after treatment for 4 weeks. Neither drug affected the levels of total protein in CSF. The results indicate that with the doses used thiothixene causes a more marked and long lasting blockade of central dopamine receptors controlling prolactin release. The study also demonstrated the versatility of using prolactin analyses of CSF and plasma as tools for quantitation of biochemical effects of neuroleptic drugs on the human central nervous system.

Key words: Prolactin – Melperone – Cerebrospinal fluid – Thiothixene – Schizophrenia – Neuroleptics.

Introduction

During the last few years several antipsychotic drugs have been shown to increase the levels of radioimmunoassayable prolactin in the plasma (Kleinberg and Frantz,

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1971; Clemens et al., 1974; Wilson et al., 1975; Frantz and Sachar, 1976; Meltzer and Fang, 1976) and the cerebrospinal fluid (CSF) (Sedvall et al., 1975; MacLeod and Login, 1977; Wode-Helgodt et al., 1977) of patients and experimental animals. The prolactin elevation represents a fairly specific pharmacodynamic effect of the neuroleptic drugs, since treatment of patients with antidepressant drugs or lithium did not result in an elevation of the prolactin levels in CSF (Sedvall et al., 1975). The prolactin elevation is, in all probability, related to the neuroleptic induced blockade of receptors for the hypothalamic dopamine neurones that inhibit prolactin release from the pituitary gland (Frantz and Sachar, 1976).

In order to compare the dopamine receptor blocking potency of different neuroleptic drugs in clinical use, the ability of various compounds to elevate prolactin levels in patients may accordingly be monitored. With regard to the current discussion of the relation between drug induced central dopamine receptor blockade and antipsychotic efficacy, it may also be of interest to compare in the same clinical setting the abilities of neuroleptic drugs to improve psychotic patients and to elevate prolactin levels, i.e. to study the relation between antipsychotic effect and blockade of dopamine receptors.

Melperone and thiothixene are two neuroleptic drugs claimed to induce therapeutic effects in psychotic patients (Schulsinger et al., 1965; Bishop et al., 1966; Gallant et al., 1966; Gross and Haberler, 1970; Jacobsson et al., 1976). These drugs have also been shown to exhibit neuroleptic effects in animal behavioral tests (Christensen et al., 1965; Weissman, 1974) and they markedly elevate levels of the major dopamine metabolite, homovanillic acid (HVA), in the brain of mice and rats (Wiesel et al., 1978). In a previous study we reported that melperone was less potent than thiothixene in elevating the level of HVA in CSF of psychotic patients (Bjerkenstedt et al., 1977). Since the elevation of the HVA concentration in CSF is generally assumed to be predominantly related to a pre- or postsynaptic blockade of receptors in the nigrostriatal dopamine system, the latter study supplied evidence that melperone is a less potent receptor blocking compound in this dopamine system than thiothixene.

In the present study we were interested in examining the relative difference between melperone and thiothixene in blocking central dopamine receptors related to the control of prolactin release. The prolactin elevation should be specifically related to blockade of receptors for the hypothalamic tubero-infundibular dopamine neurons. With the biochemical background information obtained in such a study it may subsequently be possible to examine the relationships between receptor blockades in different central dopamine systems and antipsychotic effects in drug treated psychotic patients. If significant relationships between biochemical and clinical effects induced by neuroleptic drugs can be demonstrated, they may be useful for the adjustment of optimal drug dosage in psychotic patients.

In the present study we have examined whether melperone and/or thiothixene in therapeutic doses elevate prolactin (PRL) levels in CSF and plasma of psychotic patients. We have also examined the time course for the effect and persistence of it after abrupt withdrawal of the drugs. Finally the relationships between PRL levels in CSF and plasma were examined before and after different time intervals of drug treatment.

Material and Methods

The study was performed as part of a major investigation which aimed at studying the relations between clinical and biochemical effects in psychotic patients treated with melperone or thiothixene. The protocol of the investigation was approved by the Ethical Committee of the Karolinska Institutet, Stockholm, Sweden. All the patients gave their consent to participate in the study.

Eighty-one acutely psychotic women admitted with a schizophrenic symptomatology were selected from the emergency ward according to the symptom criteria described in a previous paper (Bjerkenstedt et al., 1977). Exclusion criteria were organic brain disease, somatic disease, toxicomania, manic or depressive psychosis, and symptoms of borderline personality. The patients should not have been treated regularly with an antipsychotic drug during the month preceding the admittance. 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 had received single doses of neuroleptic drugs during the preceding month, but not within the 2 days immediately before the placebo period. The age distribution of the patients is presented in Table 1.

Administration of Drugs. During the first few days placebo tablets were administered. During this interval blood and lumbar CSF was taken and the clinical state rated according to standardized procedures (Bjerkenstedt et al., 1978). After the placebo period, melperone tablets (Buronil 100 mg) or thiothixene tablets (Navane 10 mg) were administered according to a double-blind procedure. Melperone was given to 29 patients and thiothixene to 34. The double-dummy technique was used (Bjerkenstedt et al., 1977). During the first week of active treatment the drugs were given at 8 a.m. and at 4 p.m. From the second week, the dose was increased to three tablets of the active compound as well as the placebo per day, with the additional tablets given at 12 a.m. During the remaining 3 weeks of the study, this dose was kept constant. Blood and CSF samples were taken and the clinical state rated again after active drug treatment for 2 and 4 weeks.

In order to study the variations during the day in the plasma PRL level, samples were taken from a small group of patients from each treatment group after active drug treatment for at least 10 days (doses given at 8 a.m., 12 a.m., and 5 p.m.). The sampling intervals are shown in Figure 6. To study the persistence of the drug induced effect on PRL level, plasma samples were also taken at 8 a.m. and 4 p.m. the day after the active drugs had been withdrawn. In the serum from the melperone treated patients, the levels of melperone were also determined.

Twenty-one patients (thiothixene = 12, melperone = 9) received diazepam (Stesolid, AB Dumex, Sweden) for sleep induction (5—10 mg) or sedation (5—10 mg × 4) during the study. All these patients received the drug during active neuroleptic treatment, but only five of them received diazepam also during the placebo period. Fifteen patients (thiothixene = 11, melperone = 4) also received biperiden (Akineton, AB Meda, Sweden, 5 mg × 3) during some part of the active treatment period. The data from the patients treated with diazepam and biperiden were not significantly different from those who followed the protocol strictly. Therefore, the data from all patients were pooled.

Sampling of Lumbar CSF and Blood. The samples of CSF and blood were taken at 8 a.m. when the patients had been at bed rest and fasting for 12 h. The lumbar puncture was performed with the patient in a sitting position and before the first drug dose of the day. A CSF sample of

Table 1. Patient material

Treatment	*n*	Age years	
		Mean	Range
Melperone group	29	35.6	21—59
Thiothixene group	34	40.6	19—63

12—13 ml was removed. Venous blood was drawn from an antecubital vein immediately after the CSF sample. The samples were centrifuged at 2,000 × g within 30 min and the supernatants were mixed and stored at below −20°C pending the analysis.

Determination of PRL Levels. The concentrations of prolactin-like material in CSF and plasma were measured by radioimmunoassay (RIA). A commercial kit for human prolactin from Serono, Rome, Italy, was used. All the PRL determinations were performed blindly with regard to the protocol of the investigation. The different CSF and plasma samples from each patient were analysed on the same day. All data are based on the analysis of duplicate determinations. Usually, the analysis was performed within 2 months of sampling. Storage of CSF samples for 6 months did not result in any significant diminution of the PRL level. The intra-assay variation was determined from double determinations of eight samples of CSF or plasma from untreated patients. The standard deviation for CSF was ± 20.4% and for plasma 14.0%. The standard deviation for CSF from patients treated with neuroleptics was ± 17.3% (n = 7). The inter-assay variation was determined by repeated analysis of pools of CSF and plasma from individuals that were not treated with neuroleptics. The level obtained in the pool of CSF was 1.2 ± 0.75 ng/ml (Mean ± SD, n = 8). The corresponding values for the plasma pool was 13.1 ± 1.4 ng/ml (n = 8).

Determination of Protein Levels in CSF. Total protein was determined according to Lowry et al. (1951) using tyrosine as standard.

Determination of Melperone Levels in Serum. A gas chromatographic method was used (Hultman and Stensiö, 1978).

Statistical calculation of differences of means from paired and unpaired data and correlation coefficients were computed by conventional statistical methods (*t*-tests and analysis of variance). When necessary the tests were corrected for heterogeneity of variances (Lindman, 1974). All tests except the test of correlation coefficients were two-sided.

Results

A. Pre-Treatment Levels of PRL in CSF and Plasma of Psychotic Women

In all patients but three the amount of PRL in CSF was above the blank values. The highest amount obtained in an untreated patient was 5.7 ng/ml. The levels of PRL in CSF and plasma of the psychotic women before treatment (Figs. 1—2)

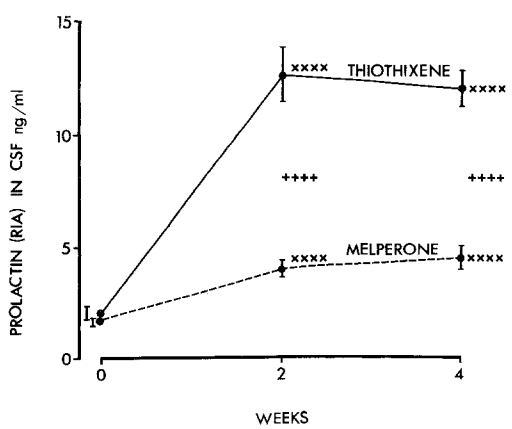


Fig. 1. PRL levels in CSF of psychotic women before and during treatment with melperone or thiothixene. The data represent mean values ± SE from at least 27 patients. ++++ $P < 0.001$ difference between treatment groups, **** $P < 0.001$ difference to pre-treatment level, *** $P < 0.01$, ** $P < 0.02$, * $P < 0.05$

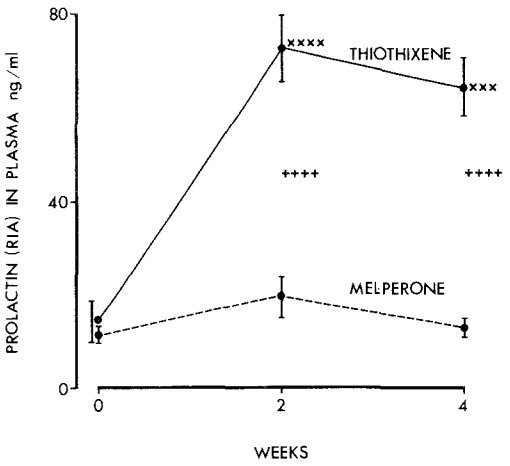


Fig. 2. PRL levels in plasma of psychotic women before and during treatment with melperone or thiothixene. The data represent mean values ± SE from at least 12 patients

were of the same order as those previously reported (Turkington, 1972; Frantz, 1973; Meltzer et al., 1974; Sedvall et al., 1975; Wilson et al., 1975; Frantz and Sachar, 1976). The PRL levels in CSF and plasma before treatment did not differ significantly between the melperone and thiothixene groups.

B. Effects of Melperone or Thiothixene on the PRL Level in CSF of Psychotic Women

In both the melperone and thiothixene treated patients the PRL levels were significantly elevated after 2 as well as 4 weeks (Fig. 1). At both time intervals, the PRL levels were significantly higher ($P < 0.001$) in the thiotixene treated patients as compared to those who received melperone. The highest PRL level, 26 ng/ml, was obtained in a thiothixene treated patient.

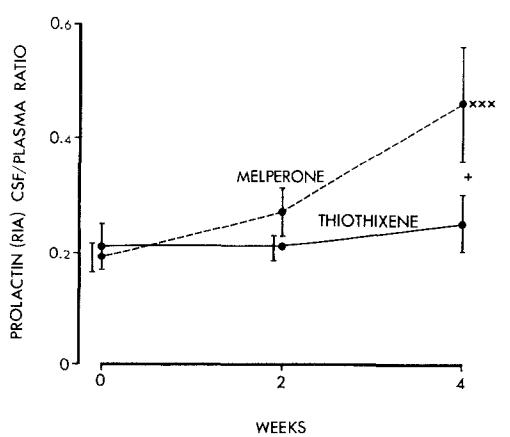


Fig. 3. The ratio between PRL levels in CSF and plasma before and during treatment with melperone or thiothixene. The data represent mean values ± SE from at least 12 patients

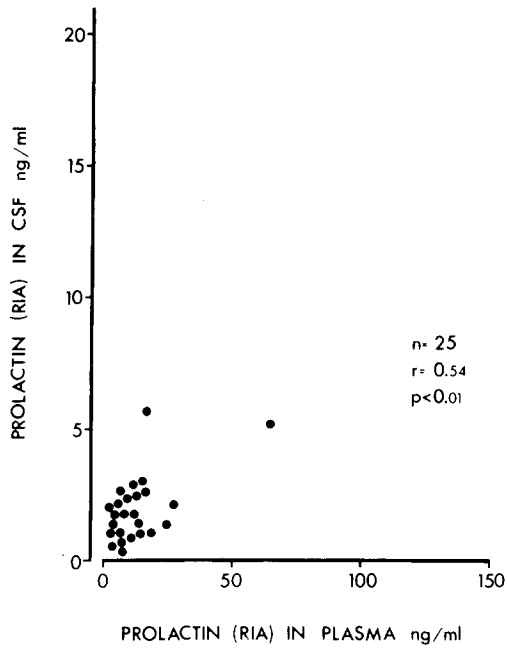


Fig. 4. Relation between PRL levels in CSF and plasma of untreated psychotic women

C. Effects of Melperone or Thiothixene on the PRL Level in Plasma of Psychotic Women

After 2 and 4 weeks of melperone treatment there was no alteration of the PRL level in plasma from samples taken at 8 a.m., i.e. 16 h after the last drug dose. During thiothixene treatment the plasma PRL level was significantly elevated at 2 as well as 4 weeks (Fig. 2). In the thiothixene group the level at 4 weeks was probably significantly lower ($P < 0.05$) than the level at 2 weeks.

D. Effects of Melperone or Thiothixene on the Ratio between PRL Levels in CSF and Plasma of Psychotic Women

Treatment with melperone resulted in a significant elevation of the ratio between PRL levels in CSF and plasma at 4 weeks (Fig. 3). Thiothixene treatment did not alter this ratio.

E. Correlations between Levels of PRL in CSF and Plasma of Psychotic Women Before and During Treatment with Melperone or Thiothixene

Before treatment, PRL levels in CSF and plasma were positively correlated (Fig. 4). At 2 weeks, a significant correlation was found in the thiothixene, but not in the melperone group. At 4 weeks, there were significant positive correlations in the melperone as well as the thiothixene group (Fig. 5).

F. Plasma Levels of PRL During and After Withdrawal of Melperone or Thiothixene Treatment

Plasma samples were taken at repeated time intervals during 1 day when treatment had continued for at least 10 days (Fig. 6 A). After melperone, plasma

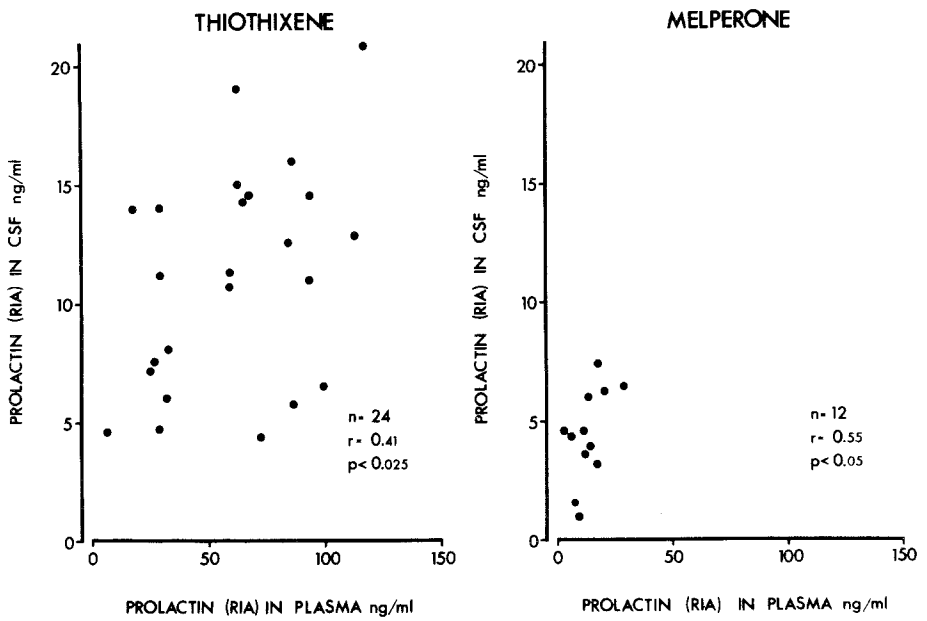


Fig. 5. Relation between PRL levels in CSF and plasma of psychotic women after treatment with melperone or thiothixene for 4 weeks

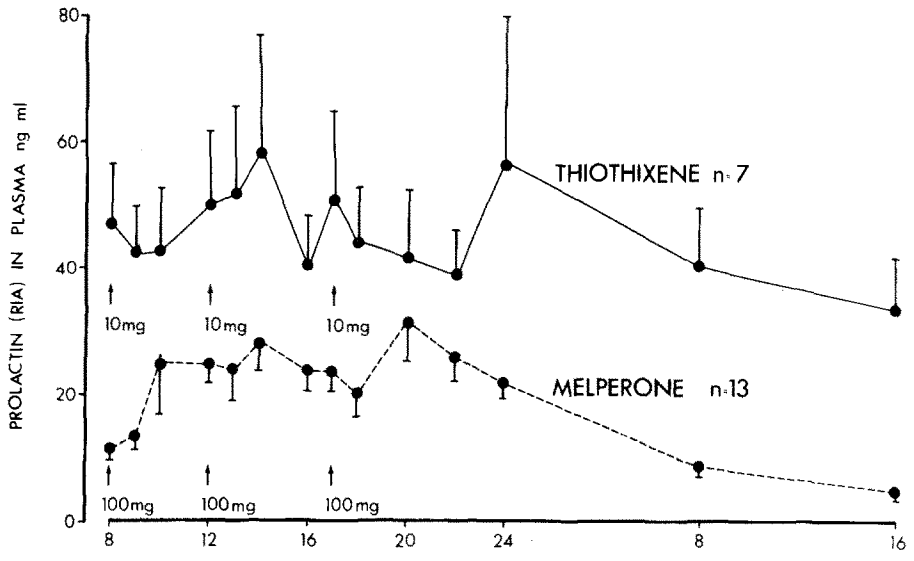
PRL levels were significantly elevated at 10 a.m. and 8 p.m. compared to the 8 a.m. level. PRL levels at 4 p.m. and 8 p.m. during treatment were also significantly higher than the 4 p.m. level the day after withdrawal.

The 4 p.m. level the day after withdrawal did not differ significantly from the pre-treatment level. In the thiothixene treated group, plasma PRL levels remained at a higher, but fairly constant level during the day before as well as the day after withdrawal.

The day after withdrawal of the drugs, the plasma PRL level at 4 p.m. was significantly higher in the thiothixene group as compared to the melperone group ($P < 0.05$). In the melperone treated patients, the plasma PRL level declined to the pre-treatment level 16 h after withdrawal. In the thiothixene treated patients, however, the plasma PRL level was significantly elevated even 23 h after withdrawal compared to the pre-treatment level.

G. Serum Levels of Melperone Before and After Withdrawal of Treatment

The concentration of melperone in serum, when treatment had continued for at least 10 days, is shown in Figure 6 B. The level followed a time course that was similar to the plasma PRL level. The average morning level of melperone during treatment (69 ng/ml) was increased by about 250% during the day to a maxium level of 203 ng/ml at 8 p.m., i.e. 3 h after the last dose of the day. The average half life of melperone in serum was about 11 h.



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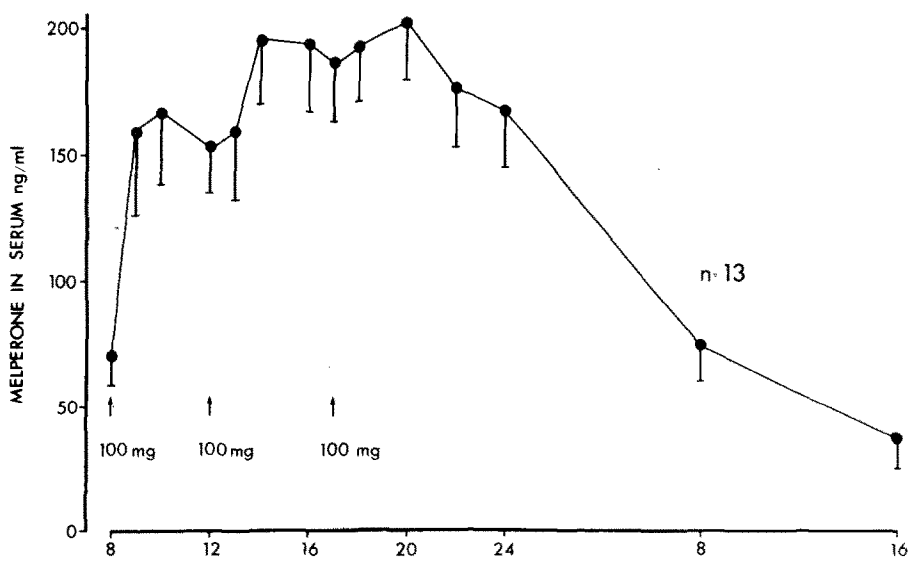

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Fig. 6. **A** Plasma levels of PRL before and during withdrawal of melperone (100 mg × 3) or thiothixene (10 mg × 3) treatment. The data represent mean values ± SE. **B** Serum levels of melperone before and during withdrawal of treatment (100 mg × 3)

Table 2. Effects of melperone or thiothixene treatment on the levels of PRL and total protein in CSF

Treatment	*n*	Parameter	Before	2 weeks	4 weeks
Melperone	8	Prolactin (ng/ml)	2.0 ± 0.28	4.6 ± 0.58****	4.6 ± 0.62****
	8	Protein (μg/ml)	402 ± 39	398 ± 37	384 ± 34
Thiothixene	21	Prolactin (ng/ml)	2.1 ± 0.24	13.9 ± 1.46****	12.1 ± 1.14****
	21	Protein (μg/ml)	392 ± 26	420 ± 28	390 ± 29

The data represent mean ± SE
**** $P < 0.001$

H. Effects of Melperone or Thiothixene Treatment on the Levels of Total Protein in CSF

In order to examine the specificity for PRL elevation in CSF, the content of total protein was also determined. As shown in Table 2, the protein level in CSF was not influenced by the drug treatment. Furthermore, there was no significant correlation between CSF levels of PRL and protein.

Discussion

Clemens and Sawyer (1974) demonstrated the presence of immunoassayable prolactin in CSF of rabbits. In an earlier preliminary study we reported a low prolactin-like immunoreactivity in CSF of non-treated psychiatric patients (Sedvall et al., 1975) and recently, the occurrence of prolactin-like material in CSF from patients with neuropsychiatric disorders and rats was confirmed (Jimerson et al., 1976; MacLeod and Login, 1977; Wode-Helgodt et al., 1977). The present study verified the occurrence of PRL in CSF of most psychotic patients. The content of PRL in CSF of untreated patients was about 20% of the plasma concentration. So far PRL has not been chemically identified and the levels in CSF of untreated patients are close to the sensitivity of the method used.

Both the antipsychotic drugs studied in the present investigation elevated the levels of PRL in CSF and plasma. This supplies pharmacological evidence that similar mechanisms control the release of CSF and plasma PRL. The immunoassayable prolactin in CSF might represent the whole prolactin molecule or immunoactive fragments of this peptide. So far it is not known how the prolactin gets into CSF. A direct transport of the peptide over the blood-brain barrier may be assumed. However, it has also been speculated that prolactin may be secreted via the tancyte ependymal cells of the third ventricle into CSF (MacLeod and Login, 1977). Whatever the mechanism that transports prolactin into CSF might be, the presence of prolactin within the central nervous system may indicate a role

for the hormone in brain function. Recently, direct evidence for the presence of prolactin sensitive neurons in the hypothalamus of rats was demonstrated (Yamada, 1975). Since the normal PRL level in CSF was close to the sensitivity of the method, calculation of the correlation between PRL levels in CSF and plasma may be erroneous. However, both before and during drug treatment significant positive correlations were found (Figs. 4—5) although there were marked individual differences in the ratio between CSF and plasma PRL levels.

Interestingly enough, when morning samples were obtained, melperone treatment resulted in an elevation of the PRL level in CSF, but not in plasma (Figs. 1—2). This discrepancy may indicate that different mechanisms regulate CSF and plasma prolactin levels and that effects of melperone on the human central nervous system persist at a time when peripheral effects have disappeared. It is possible that differences in the turnover of prolactin in CSF and plasma explain these results and the lack of correlation between the PRL levels in CSF and plasma when melperone treatment had continued for 2 weeks. The latter view is supported by experimental studies in rats by MacLeod and Login (1977). They found a longer half-life of radio-labelled prolactin in CSF than in plasma of rats. Thus, the half-life of prolactin in CSF was 118 min as compared to 18 min in plasma. These marked differences indicate the existence of efficient enzymatic mechanisms for inactivation of plasma prolactin. Such mechanisms may not be available in CSF. The high molecular weight of prolactin (ca. 20,000 daltons) will probably be an obstacle to its rapid removal from CSF. Thus, during melperone treatment the PRL level in plasma was elevated during the day (Fig. 6 A), but during the night it fell to the pre-treatment range, probably because of insufficient dopamine receptor blockage to maintain PRL secretion and rapid inactivation of the hormone in plasma. The elevated PRL level in plasma during the day may have been sufficient to force PRL into CSF. If the removal of prolactin from CSF is less efficient than in plasma, one may expect the CSF prolactin level to build up slowly. This may have been the case since the mean PRL level in CSF after treatment for 4 weeks was higher than the level after 2 weeks. Thus, the slow turnover of prolactin in CSF may explain the persistence of PRL elevation in CSF, but not plasma.

PRL levels in CSF and plasma of our untreated psychotic patients were in the same range as those found in healthy volunteers (Wode-Helgodt et al., 1978). Therefore, our data give no indication for any relation between psychotic psychopathology and a perturbated prolactin system either in the periphery or in the brain. These findings support and extend the conclusions of Meltzer et al. (1974), Sedvall et al. (1975) and Wode-Helgodt et al. (1977).

Like other antipsychotic drugs, melperone and thiothixene elevated the PRL levels in CSF and plasma indicating that both drugs block the receptors of the tubero-infundibular dopamine neurons that control prolactin release. At the fixed doses used, thiothixene was more potent than melperone. It is of interest to note that thiothixene was also more potent than melperone in elevating the level of HVA in CSF (Bjerkenstedt et al., 1977). Since the latter effect is generally considered to be related to receptor blockage in the striatal dopamine synapses, the present results indicate that the hypothalamic and striatal dopamine receptors

in the human brain respond similarly to the neuroleptic drugs studied here. The data obtained in the present study also demonstrate that there is no marked tolerance to the effects of the two drugs on the prolactin systems. Thus, the PRL levels in CSF and plasma were about the same after treatment for 2 as well as 4 weeks. This is in accordance with the data of Meltzer and Fang (1976) and Wode-Helgodt et al. (1977). The latter authors studied the effect of different phenothiazine derivatives. The higher CSF/plasma PRL ratio at 4 weeks in the melperone treated patients as compared to the thiothixene treated patients (Fig. 3) is, in all probability, due to the above mentioned short lasting effect of melperone on plasma PRL coupled to the slow removal of the hormone from CSF.

Thiothixene and melperone have both been shown to improve schizophrenic patients. The present and our previous study (Bjerkenstedt et al., 1977) indicate that both drugs block hypothalamic and striatal dopamine receptors in such patients. These results are compatible with a relationship between the central dopamine receptor blockage and the antipsychotic effect. With the doses used, thiothixene induced the most marked effects on the PRL levels. It can accordingly be assumed that the brains of thiothixene treated patients were subjected to higher PRL concentrations and greater dopamine receptor blockage than those of the melperone treated patients. If there is a causal relationship between the effects on the prolactin systems and/or the receptor blockage and the antipsychotic effects of the two drugs examined, one may expect thiothixene to be a better antipsychotic agent than melperone. However, the clinical evaluation of the therapeutic effects of the two drugs gave no indication of a superiority for thiothixene over melperone (Bjerkenstedt et al., 1978). Our results may accordingly be interpreted as evidence against a direct role for a prolactin-like compound or general dopamine receptor blockade for the antipsychotic efficacy of the neuroleptics used in this study. However, it can not be excluded from the present data that only a small effect on the prolactin system and/or dopamine receptors may be sufficient for the manifestation of maximal therapeutic effects. Therefore, a further analysis of the quantitative relation between the receptor blockage in the various central dopamine systems and the antipsychotic effect of neuroleptics is required.

The present study demonstrated the versatility of using prolactin analysis of CSF and plasma as tools for the quantitation of biochemical effects of neuroleptic drugs on the human central nervous system. Quantitative differences between the effects of the two drugs examined were found. The relations between the biochemical effects found here and the antipsychotic effects of the drugs merit further investigations.

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