Prolactin in cerebrospinal fluid and dopamine function in man

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Evidence from animal studies and limited data in man indicate that plasma prolactin and other neuroendocrine hormones may be under relatively direct influence of biogenic amine transmitters in the central nervous system (Meites, Lu & others, 1972; DeWied & DeJong, 1974). The present study explores the possibility that prolactin concentrations in lumbar cerebrospinal fluid (csf) might provide a new source of data on central dopamine function in patients. Based on plasma studies, one would expect that csf prolactin concentration, if reliable, should decrease with central dopamine receptor stimulation (Lal, de la Vega & Sourkes, 1973), and should rise with dopamine receptor blockade (Kleinberg, Noel & Frantz, 1971). In studies of dopamine-active drugs in psychiatric patients, lumbar csf measurements of homovanillic acid (HVA), a major metabolite of central dopamine in man, have provided the most direct index of altered dopamine metabolism (Goodwin & Post, 1975). Drug-induced alterations in csf HVA accumulations have been demonstrated and are thought to reflect feedback control of presynaptic dopamine 'turnover'—i.e., transmitter synthesis, release, and degradation (Goodwin, Post & others, 1973). To the extent that csf prolactin concentrations reflect alterations in post-synaptic dopamine receptor activity they may represent a more direct index of dopamine function than HVA accumulations. In a preliminary evaluation of this possibility, we have studied the effects of piribedil, a relatively specific dopamine receptor agonist (Corrodi, Fuxe & Ungerstedt, 1971), and of pimozide, a relatively specific dopamine receptor blocker (Andén, Butcher & others, 1970), on csf prolactin concentrations in depressed patients.

Csf prolactin concentrations were measured in depressed patients in a clinical research unit at the National Institute of Mental Health. Patients met criteria for primary affective illness or schizo-affective illness (Spitzer, Endicott & Robins, 1975), were in good physical health, and adhered to a low monoamine diet. Lumbar punctures were made in eight patients following two weeks free of medication, and were repeated in four patients during extended (2–5 weeks) administration of piribedil (up to 240 mg day^{-1}), and in four other patients during brief (5–7 days) and extended (2–4 weeks) administration of pimozide (4 mg day^{-1}). Lumbar punctures were done at bedrest at 3:00 pm after administration of probenecid (100 mg kg^{-1}) in divided oral doses. Probenecid inhibits the transport system responsible for the removal of acid metabolites from csf, and provides an estimate of central dopamine turnover (Goodwin & others, 1973).

Csf prolactin concentrations were assayed in duplicate by homologous double-antibody radioimmunoassay (Rogol & Rosen, 1974), on the fourteenth ml of csf collected in each lumbar puncture, using prolactin standard VSL-II (courtesy of Hormone Distribution Program, NIAMDD) and antiserum RB-4 (courtesy of Dr Judith Vaitukaitis, NICHD). All samples were run in a single assay. HVA was assayed by a fluorometric technique, as previously described (Goodwin & others, 1973).

In the depressed patients, csf prolactin concentrations were consistently measurable, ranging from 5·9 to 7·7 ng ml^{-1}, with a mean of 6·6 ng ml^{-1}. These concentrations were approximately 35% of the 1:00 pm plasma prolactin concentrations (mean = 18·0 ± 1·0 ng ml^{-1}) previously measured during neuroendocrine blood studies in 10 clinically similar, drug-free depressed patients at bedrest (Jimerson, Post & others, 1976). The csf prolactin concentration was not significantly related to age, sex, or severity of depression in the 8 patients studied. Comparison of prolactin concentrations with HVA accumulations following probenecid in these patients yielded a non-significant negative correlation ($r = -0.56$).

In the four patients studied during extended treatment with piribedil (Fig. 1), there was a consistent decrease in csf prolactin concentrations compared to drug-free levels ($P < 0.05$ by paired t-test). In the three patients in whom we simultaneously measured csf HVA, there was again a consistent decrease in the metabolite, presum-

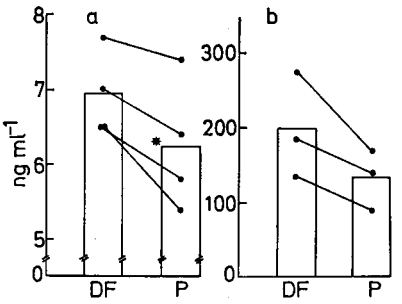

FIG. 1. The effect of piribedil on a-prolactin and b-homovanillic acid (HVA) in cerebrospinal fluid (csf) in depressed patients. The decrease in csf prolactin is significant, $P < 0.05$, by paired t-test.

During recent studies with different prolactin standard (Calbiochem lot 628007) and antiserum VSL-II (courtesy of Hormone Distribution Program, NIAMDD), prolactin has often been undetectable in csf.

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ably on the basis of feedback inhibition of presynaptic dopamine activity, and in agreement with the previous report by Chase & Shoulson (1975). In the four patients treated with pimozide, there was a significant increase in csf prolactin (control $6 \pm 0{\cdot}5$ ng ml^{-1}) at both the brief (5–7 days, $12{\cdot}0 \pm 1{\cdot}0$ ng ml^{-1} $P < 0{\cdot}05$) and extended (2–4 weeks, $10{\cdot}5 \pm 0{\cdot}5$ ng ml^{-1} $P < 0{\cdot}01$) time-points, compared to the drug-free concentrations. In these four patients, HVA accumulations were not significantly altered by pimozide treatment compared with drug-free values.

The consistently measurable prolactin concentrations in lumbar csf in depressed patients reported here confirms a similar report in a mixed psychiatric population by Sedvall, Alfredsson & others (1975), although in this study and in two other recent reports (Kendall, Seaich & others, 1975; Schroeder, Johnson & Malarkey, 1975), mean csf prolactin concentrations were less than 2 ng ml^{-1}. Further study is required to evaluate the possibility that depressed patients may have higher csf prolactin than other diagnostic groups; or that csf aliquot, stress, or inter-assay variability may account for this difference in concentration. Our preliminary results in several patients indicate that csf prolactin did not rise with probenecid administration in comparison with non-probenecid lumbar punctures. The question of the origin and mode of entry of prolactin into csf remains unanswered, as do the possible importance of transport mechanisms or a ventricular to lumbar csf concentration gradient. The permeability of the blood-brain and blood-csf barriers to prolactin in man, and the functional relation between csf and blood concentrations of the hormone remain to be explored. Preliminary data of Kendall & others (1975) suggest that the related polypeptides ACTH and growth hormone do not readily cross the blood-csf barrier in man, despite other evidence that rat prolactin crosses into the csf when administered intravenously to rabbits (Clemens & Sawyer, 1974). The possible functional importance of prolactin in human csf is also unknown, although recent data on the presence of hypothalamic releasing factors in csf (Barbato, Lawrence & Kirsteins, 1974) and their absorption by the ependymal cells of the median eminence (Porter, Ben-Jonathan & others, 1975) support the possibility that csf may be an active link in the central neuroendocrine regulatory system.

The data presented demonstrate that dopamine-active drugs produce predictable changes in csf prolactin, and that these alterations are in the same direction as the plasma prolactin responses to similar compounds. The decrease in csf prolactin with piribedil apparently reflects direct dopamine receptor stimulation by the drug, while the concomitant decrease in HVA accumulations may represent a secondary decrease in dopamine synthesis. Increased csf prolactin in the pimozide-treated patients would be compatable with dopamine receptor blockade, even though the HVA accumulations were not consistently elevated (as has been reported in other studies of patients on neuroleptics (Post & Goodwin, 1975)). Sedvall, Alfredsson & others (1975) have recently shown that other neuroleptics also increase csf prolactin. The present data suggest, then, that csf prolactin response may provide a relatively direct and sensitive index of pharmacologically-induced alterations in central dopamine receptor activity.

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