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Depletion of Glutathione and enhanced lipid peroxidation in the CSF of Acute Psychotics following haloperidol administration.

Abstract
Haloperidol administration for 2 weeks results in significant reduction in the concentration of GSH in the CSF. Concomitantly, the levels of lipid peroxidation products increased as evidenced by increased malondialdehyde levels. The malondialdehyde levels in the CSF prior to haloparidol administration were not significantly higher than that seen in CSF from normal controls (data not shown) suggesting that increased oxidative stress did not exist in these patients prior to haloperidol administration. All the patients included in the present study were drug naive and hence the changes observed in the glutathione and malon6ialdehyde levels in the CSF were indeed mediated by haloperidol administration. The only other medication that was administered namely, anticholinergic drug, trihexyphenidyl is not known to cause any oxidative stress. The present study thus demonsuates that haloperidol administration results in significant oxidative stress. The generation of the oxidative stress is probably due to the increased turnover of dopemine caused by typical neuroleptics. Increased dopamine turnover is also observed in Parkinson's disease and the combination therapy consisting of antioxidant vitamin E and monoamine oxidase inhibitor, deprenyl has been shown to offer limited protection against the progression of the disease (Parkinson Disease Study Group 1989). In the present study, all the 15 patients exhibited extrapyramidal symptoms although the time of onset, the duration and the severity of the side effects differed between patients. On the presumption that the oxidative stress generated by haloperidel may cause extrapyramidal symptoms, the present study in humans taken together with the evidence provided in our earlier studies on rats (Shivakumar and Ravindranath 1992,1993) may justify experimental coadministration of antioxidanls (e.g., vitamin E) with typical neuroleptics like haloperidol to prevent the acute side effects.

Keywords
enhanced, glutathione, csf, following, lipid, peroxidation, acute, administration, depletion, haloperidol, psychotics

Disciplines
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Depletion of Glutathione and Enhanced Lipid Peroxidation in the CSF of Acute Psychotics Following Haloperidol Administration

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Key words: Glutathione, haloperidol, neuroleptics, oxidative stress, cerebrospinal fluid, acute psychosis

Introduction

The usage of typical neuroleptic drugs has been limited by the side effects and toxicity produced by them. The major side effects are the range of extrapyramidal symptoms including neuroleptic malignant syndrome and tardive dyskinesia. The pharmacological action of neuroleptics is associated with their antagonist action on dopamine receptor. The blockade of dopamine receptors by neuroleptics leads to increased turnover of dopamine as demonstrated by increased levels of the dopamine metabolite, homovanillic acid in the cerebrospinal fluid (Scatton et al 1977). Dopamine is metabolized by monoamine oxidase (MAO) as given below:

$$\text{Dopamine} + \text{Oxygen} + \text{Water} \xrightarrow{\text{MAO}} \text{Hydrogen Peroxide} + \text{Ammonia} + \text{3,4 Dihydroxy phenylacetaldehyde}$$

Hydrogen peroxide is a potent oxidant and can react with iron (Fe^{2+}) or copper (Cu^{2+}) to form the highly toxic hydroxyl radical. Reactive oxygen species such as hydrogen peroxide and hydroxyl radical react extensively with cellular constituents leading to oxidative damage to proteins, lipids, and deoxyribose nucleic acid (DNA). The hydroxyl radical can set up a chain reaction leading to peroxidation of lipids thus damaging the integrity of cell membranes (Halliwell 1992).

Acute (Shivakumar and Ravindranath 1992) and chronic (Shivakumar and Ravindranath 1993) administration of haloperidol (a neuroleptic belonging to the class of butyrophenones) to rats resulted in the generation of significant oxidative stress in brain regions as evidenced by the loss of the nonprotein thiol antioxidant glutathione (GSH) and increase in the lipid peroxidation product, malondialdehyde. The depleted GSH is essentially recovered as protein-GSH mixed disulfide and the oxidized GSH (GSSG) levels were not elevated substantially. Extensive modification of the protein thiols was also detected, which could be attributed to the formation of protein glutathione mixed disulfides and protein mixed disulfides. Because GSH is responsible for the maintenance of protein thiol homeostasis in the cell, the depletion of GSH levels also contributes to the disturbance in the protein thiol homeostasis.

The generation of oxidative stress in humans by haloperidol administration is yet to be demonstrated although it has been hypothesized that the toxic side effects seen in man may be due to the generation of oxidative stress caused by increased dopamine turnover (Cadet et al 1986). In an earlier study, Pall et al observed that phenothiazines increased lipid peroxidation in the cerebrospinal fluid (CSF) of a diagnostically heterogeneous group of patients (Pall et al 1989). Coadministration of vitamin E with haloperidol resulted in some beneficial effect in patients with tardive dyskinesia (Lohr et al 1988). Two recent studies have reported little or no beneficial effect of antioxidant therapy in tardive dyskinesia (Shriqui et al, 1991 and Egan et al 1991), however, to our knowledge, no information is available on the antioxidant status following administration of haloperidol.

In the present study, the concentration of GSH and the lipid peroxidation product, malondialdehyde were estimated in the CSF of drug-naive acute psychotic patients before and after 2 weeks of haloperidol administration.

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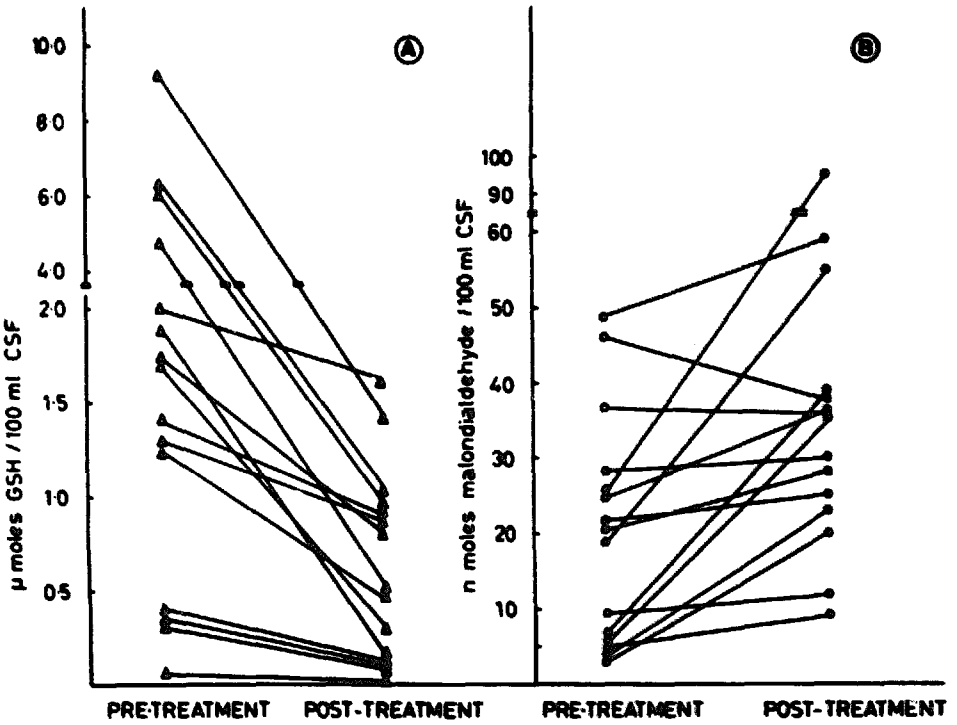

Figure 1. The concentration of (A) glutathione and (B) malondialdehyde in the CSF of patients before and after haloperidol administration. Glutathione levels were measured in the CSF before (△) after (▲) haloperidol administration. The levels of malondialdehyde were also determined before (○) and after (●) haloperidol treatment.

Methods

Patients

Inpatients of both the sexes aged 17–40 years who met the diagnostic criteria for acute and transient psychosis (F23) of the ICD-10 (World Health Organization 1990) formed the sample of the study. Informed consent was obtained from the patients for (1) the inpatient stay of at least 2 weeks, (2) treatment with haloperidol, and (3) two lumbar punctures before and after haloperidol administration for 2 weeks. No patient had clinical evidence of nutritional deficiency, neurological illness, or associated infections. None of the patients had a history of alcohol or substance abuse and none had received neuroleptics or electroconvulsive therapy before. Routine investigations that included blood counts, fasting blood sugar, serum cholesterol, liver and renal function tests were normal in all the patients. Similarly, patients had normal blood vidal test and serological tests for syphilis.

Patients received oral haloperidol (10 mg/day) for a period of 2 weeks. The anticholinergic drug, trihexyphenidyl (2–4 mg/day) was administered to all the patients only when the patients manifested extrapyramidal symptoms impairing their daily activities. The anticholinergic drug was introduced at varying time points during the 2-week period of haloperidol therapy. No other medication was used during the first 2 weeks of haloperidol treatment.

Assessment

The psychopathology of the patients was rated using the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962) before treatment and after 1 and 2 weeks of treatment. Before haloperidol administration was started, and after 2 weeks of haloperidol treatment, CSF was collected by lumbar puncture between the L_3–L_4 disc spaces. CSF samples were aliquoted and two aliquots were frozen immediately and stored at −20°C. GSH levels in the CSF were estimated using the enzymatic recycling method (Tietz 1969) and malondialdehyde was estimated as thiobarbituric acid reactive products (Ohkawa et al 1979). All biochemical analyses were carried out blind to patient status. One aliquot of the CSF was used for the estimation of protein, glucose, and cell count, which was carried out on the same day as the lumbar puncture. Only patients with normal CSF (as evidenced by normal cell count, protein, and glucose levels) were included in the study and continued to receive haloperidol for 2 weeks. Thereafter, another lumbar puncture was performed and the CSF was collected and used as before. The patient group was comprised of 15 individuals (8 women) with mean age (SD) of 26.7 (6.8) years. The mean (SD) duration of illness was 11.2 (7) days. Significant reductions in BPRS scores from a mean (SD) of 37.3 (4.2) to 22.4 (3.2) was observed at the end of the 2 weeks of treatment.

Results

The GSH levels in the CSF decreased significantly after 2 weeks of haloperidol administration. The average decrease in GSH levels was 76% as compared to pretreatment levels. The mean GSH levels in the CSF were 2.6 (0.7) and 0.6 (0.13) μmoles/100 ml before and after haloperidol administration, respectively. The de-

crease in GSH levels was noted in all the patients included in the study and it varied between 93% to 21% depletion. Concomitant with the GSH decrease, the CSF malondialdehyde levels (indicative of lipid peroxidation products) increased after haloperidol administration. The average increase was 86% as compared to pretreatment levels. The mean (SEM) malondialdehyde levels were 20.0 (4.0) and 36.2 (5.5) nmoles of malondialdehyde/100 ml CSF before and after haloperidol administration. The increase in malondialdehyde ranged from 105% to 625% of the pretreatment levels. In 2 out of the 15 sets of samples analyzed, no increase was observed in malondialdehyde levels after haloperidol administration (Figure 1).

Discussion

Haloperidol administration for 2 weeks results in significant reduction in the concentration of GSH in the CSF. Concomitantly, the levels of lipid peroxidation products increased as evidenced by increased malondialdehyde levels. The malondialdehyde levels in the CSF prior to haloperidol administration were not significantly higher than that seen in CSF from normal controls (data not shown) suggesting that increased oxidative stress did not exist in these patients prior to haloperidol administration. All the patients included in the present study were drug naive and hence the changes observed in the glutathione and malondialdehyde levels in the CSF were indeed mediated by haloperidol administration. The only other medication that was administered namely, the anticholinergic drug, trihexyphenidyl is not known to cause any oxidative stress.

The present study thus demonstrates that haloperidol administration results in significant oxidative stress. The generation of the oxidative stress is probably due to the increased turnover of dopamine caused by typical neuroleptics. Increased dopamine turnover is also observed in Parkinson's disease and the combination therapy consisting of antioxidant vitamin E and monoamine oxidase inhibitor, deprenyl has been shown to offer limited protection against the progression of the disease (Parkinson Disease Study Group 1989).

In the present study, all the 15 patients exhibited extrapyramidal symptoms although the time of onset, the duration and the severity of the side effects differed between patients. On the presumption that the oxidative stress generated by haloperidol may cause extrapyramidal symptoms, the present study in humans taken together with the evidence provided in our earlier studies on rats (Shivakumar and Ravindranath 1992, 1993) may justify experimental coadministration of antioxidants (e.g., vitamin E) with typical neuroleptics like haloperidol to prevent the acute side effects.

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