Pharmacological Study of Protein Malnutrition on the Pharmacological Profile of Certain Antipsychotic Drugs in Experimental Animals

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(Pharmacology & Toxicology)

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SUMMARY AND CONCLUSIONS

In the present study, the effects of protein malnutrition alone and in presence of clozapine (20 mg/kg), as well as haloperidol (2 mg/kg) were studied in rats after 2 hours, 7 and 14 days on behavioral and biochemical parameters.

Protein malnutrition was induced by restricting the amount of casein in the prepared diet to 7.5% instead of 20% protein in normal diet. Feeding on low protein diet started just after weaning period.

Three models of behavioral experiments were selected to study the possible effects of protein malnutrition on behavioral responses to the chosen drugs. These models included Swimming test, Open field test and Conditioned avoidance test.

In addition, biochemical parameters were measured in the brain namely serotonin, noradrenaline, dopamine and gamma-aminobutyric acid.

The main findings of this study can be summarized as follows:-

I) Behavioral Tests

a- Swimming Test:-

1) Protein malnutrition increased swimming time and did not affect the latency time and direction score.
2) Repeated administration of clozapine (20 mg/kg) decreased swimming time after 7 and 14 days in both normally-fed and protein malnourished rats. It decreased latency time after 14 days in normally-fed rats.
3) Protein malnutrition has no effect on the action of clozapine on all measured parameters of the swimming test.

4) Repeated administration of haloperidol has no effect on all measured parameters of the swimming test.
5) Protein malnutrition has no effect on the action of haloperidol on all measured parameters of the swimming test.

b- Open Field Test

1) Protein malnutrition decreased ambulation frequency, rearing frequency, self grooming and field sniffing behavior.
2) Repeated administration of clozapine (20mg/kg) increased latency time after 7 days of drug administration while it decreased latency time after 14 days of drug administration as compared to the effect after 7 days in normally-fed rats.
3) Repeated administration of clozapine for 14 days decreased latency time as compared to its action after 7 days in protein malnourished rats
4) Protein malnutrition increased the effect of clozapine on latency time after 2 hours of drug administration
5) Repeated administration of clozapine for 7 days increased ambulation frequency and field sniffing in both normally-fed and protein malnourished rats.
6) Repeated administration of clozapine for 14 days increased field sniffing in protein malnourished rats
7) Protein malnutrition increased the effect of clozapine on field sniffing after 14 days of drug administration
8) Repeated administration of haloperidol (2mg/kg) for 7 days increased ambulation frequency in normally-fed rats and decreased latency time, rearing frequency and field sniffing in protein malnourished rats.

9) Repeated administration of haloperidol (2mg/kg) for 14 days decreased ambulation frequency as compared to its action after 7 days and rearing frequency in normally-fed rats. It increased latency time, ambulation frequency and field sniffing after 14 days of drug administration in protein malnourished rats.
10) Protein malnutrition increased the effect of haloperidol on latency time after 2 hours and 14 days and rearing frequency after 14 days only.
11) Protein malnutrition decreased the effect of haloperidol on ambulation frequency and field sniffing after 7 days of drug administration

c- Conditioned Avoidance Test

1) Protein malnutrition decreased learning ability but didn't affect retrieval ability.
2) Repeated administration of clozapine (20mg/kg) has no effect on percentage failure to avoid electric shock.
3) Protein malnutrition has no effect on the action of clozapine on percentage failure to avoid electric shock.
4) Repeated administration of haloperidol (2mg/kg) for 14 days increased the percentage failure to avoid electric shock in normally-fed rats as compared to the action after 7 days and in protein malnourished rats as compared to the action after 2 hours and 7 days.
5) Protein malnutrition increased the action of haloperidol on percentage failure to avoid electric shock after 2 hours, 7 and 14 days.

II)Biochemical Tests

1) Protein malnutrition decreased serotonin, norepinephrine and dopamine but increased GABA brain content.
2) Repeated administration of clozapine for 7 days increased brain NE content in both normally-fed and protein malnourished rats. It decreased brain dopamine content in both normally-fed and protein malnourished rats. Similarly it decreased brain GABA content in normally-fed rats.
3) Repeated administration of clozapine for 14 days increased brain NE content in both normally-fed and protein malnourished rats and decreased brain dopamine content in protein malnourished rats. Similarly it decreased brain GABA content in normally-fed rats.
4) Protein malnutrition decreased the action of clozapine on brain NE and dopamine contents after 14 days of drug administration.
5) Protein malnutrition increased the action of clozapine on brain GABA contents after 2 hours, 7 and 14 days of drug administration.
6) Repeated administration of Haloperidol for 7 days decreased brain serotonin and GABA contents in normally-fed rats. It decreased brain NE content in protein malnourished rats. It increased brain dopamine content in normally-fed rats.
7) Repeated administration of Haloperidol for 14 days increased brain NE content as compared to the action after 7 days of drug administration. It increased brain dopamine content in both normally-fed and protein malnourished rats while it decreased brain serotonin content in protein malnourished rats and brain

GABA content in both normally-fed and protein malnourished rats.

8) Protein malnutrition decreased the action of haloperidol on brain serotonin, norepinephrine, dopamine and GABA contents after 2 hours of drug administration. It decreased only the action of haloperidol on brain norepinephrine and dopamine contents after 7 days of drug administration.
9) Protein malnutrition decreased the action of haloperidol on brain serotonin, norepinephrine and dopamine contents after14 days of drug administration.

CONCLUSIONS:-

Depending on the results of the present study, it could be concluded that:-

1. Protein malnutrition decreases motor activity and learning ability but does not affect retrieval ability in rats.
2. Protein malnutrition decreases brain monoamines but increases brain GABA content.
3. Clozapine decreases motor activity and retrieval ability in both normally-fed and protein malnourished rats.
4. Protein malnutrition has no effect on the action of clozapine on motor activity and retrieval ability.
5. Clozapine decreases brain norepinephrine and dopamine contents in normally-fed rats and, to a greater extent, in protein malnourished rats.

   It follows that protein malnutrition synergizes the effect of clozapine on norepinephrine and dopamine after 14 days of drug administration.

6. Haloperidol decreases motor activity and retrieval ability in normally-fed and, to a greater extent, in protein malnourished rats. It follows that protein malnutrition synergizes the effect of haloperidol on motor activity and retrieval ability.
7. Haloperidol increases serotonin, dopamine and GABA contents in the brain of normally-fed rats.
8. Protein malnutrition antagonizes the action of haloperidol on its action on serotonin, dopamine and GABA in the brain.
9. Haloperidol decreases norepinephrine content in the brain of normally-fed rats.
10. Protein malnutrition synergizes the effect of haloperidol on norepinephrine content in the brain.