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# STUDY ON DIFFERENCES IN PHARMACOLOGICAL EFFECTS OF ANTIPSYCHOTICS IN NORMAL AND HYPERGLYCEMIC STATE

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## ABSTRACT

Significant changes were observed previously in the transport of many drugs across cell membrance due to changes in the levels of endogenous insulin. In present study the pharmacological effects of antipsychotic drugs belonging to different classes are studied on openfield activity of normal and diabetic rats. The effects that occurred due to diabetes, due to drugs, and due to drug and diabetes interaction were observed and compared statistically. Significant differences were noted in the openfield activity of normal and diabetic rats after treatment with Fluphenazine and Clopixol.

## INTRODUCTION

The antipsychotic drugs had great impact in the treatment of psychosis in general and schizophrenia in particular. They have beneficial effects on mood and thought, but carry the risk of producing side effects that mimic neurological diseases. These drugs have provided not only the most efficacious form of treatment for schizophrenia but also a unique pharmacological probe for discerning its pathophysiology. Significant research has been done regarding their mode of action, their effects on various systems and their role in different body activities.

All clinically active antipsychotic drugs share the ability to block postsynaptic dopamine (DA) receptors in the central nervous system (CNS), despite the fact that there is diversity in the chemical structure of drugs.

The antipsychotics can be classified into three pharmacological sub-groups: butyrophenones (e.g., haloperiodol)with affinity for D-2 receptors; phenothiazines (e.g., fluphenazine and perphenazine) with affinity for both D-2 and D-1 receptors but with preference for the D-2 receptors;and thioxanthines (e.g., cis(Z)- flupentixol and cis(Z)-clopenthixol) with equal affinity for D-1 and D-2 receptors (Christensen et al., 1985).

The antipsychotics are classified into typical and atypical drugs on the basis of their affinity towards 5HT-2 and DA D-2 receptors. It is stated that atypical clozapine type

antipsychotics have greater affinity towards 5HT-2 and D-2 receptors. While the typical antipsychotics are equipotent at both receptors (Stockmeier et al., 1993).

The antipsychotics are also used either alone or in combination to relieve the pain associated with diabetic neuropathy (Davis et al., 1977). In insulin dependent diabetics with symptomatic peripheral neuropathy, the amitriptyline alone or in combination with fluphenazine-HCl appeared effective in treating the discomfort within 48 to 72 hours (Battla et al., 1981). The combination of fluphenazine and amitriptyline was also found effective in treating the severe pain in extremities in patients of renal insufficiency (Mitas et al., 1983). This combination was also useful in diabetic neuropathic cachexia (Gade et al., 1980).

Neuroleptic drugs also produce endocrine changes by acting on the hypothalamus or pituitary. Most prominently neuroleptic drugs increase the secretion of prolactin in human beings (Bitton and Schneider 1992). The effects of neuroleptics on other hypothalamic neuroendocrine functions are much less characterized. Chlorpromazine impairs glucose tolerance and insulin release to a clinically appreciable degree in some pre-diabetic patients. This effect is not known to occur with other neuroleptics (Baldessarini 1996). But recently it is reported that, clozapine an atypical antipsychotic, also interferes with diabetes. It is associated with exacerbation of pre-existing diabetes mellitus. It is stressed that patients with family history of diabetes mellitus may need close monitoring of blood sugar during initiation of clozapine treatment (Popli Anand et al., 1997).

It is said that insulin increases the velocity of penetration across the cell membrane of many drugs, as well as their tissue level and potency. It was observed that the diabetic or hyperglycemic animals showed reduction in depressive effects of chlorpromazine (CPZ) as compared to normal animals upon administration. The study showed the influence of CPZ on the conditioned avoidance reflexes in rats with alloxan-diabetes. It was noted that in normal animals the CPZ caused a decrease in the number of positive reactions in proportion to increased dose. But in diabetic animals the CPZ did not evoke any inhibitory effects when given in same doses (Wizinewski and Buzcko, 1967).

In present study the difference in the openfield activity of normal and diabetic rats after the administration of different antipsychotics was investigated while comparing the animals with their respective normal and diabetic controls.

## MATERIALS AND METHODS

### *Animals:*

Locally bred female Albino Wistar rats weighing 150-200g were used, purchased from H.E.J. Research Institute of Chemistry. Before conducting the experiment the animals were given a period of acclimatization of at least five days to the laboratory conditions with 12h light/12h dark schedule. The animals were housed in group of 6 in standard metal and glass cages with free access to food and water.

***Drugs and Chemicals:***

(a) Alloxan tetrahydrate(Fluka Chemika)
(b) Antipsychotics used in the experiment are:

1. Chlorpromazine 50mg/2ml (Largactil from Rhone-Poulenc]
2. Haloperidol 5mg/ml [Serenace from Searle]
3. Fluphenazine decanoate 25mg/ml [Modecate from Bristol-Myers Squib]
4. Zuclopenthixol acetate 50mg/ml [Clopixol-Acuphase from Lundbeck].

***Experimental Diabetes:***

For the induction of diabetes, Alloxan (150mg/kg) was used by the method described elsewhere by Akhtar et al. (1981). The rats which exhibited blood sugar level of 200-350mg/dl were considered diabetic and used in experiment.

***Experimental Protocol:***

For each drug there are two major groups. And each major group has two sub-groups.

| 1- NORMAL | | 2- DIABETIC | |
|---|---|---|---|
| Control | (n=6) | Control | (n=6) |
| Test | (n=6) | Test | (n=6) |

The control animals of both groups received saline (0.9% NaCl), while the test group received the test drug.

After 30 minutes (min) of injection in case of chlorpromazine and haloperidol, and after 45 min. in case of fluphenazine and clopixol openfield activity was observed.

***Openfield Activity:***

The openfield apparatus used in the present study consisted of a square area 76x76 cm with walls 42cm high. The floor was divided by lines into 25 equal squares. The rats were exposed to the openfield after 30min. and 45min of receiving injection. To determine openfield activity a saline injected rat was placed for the first time in the center square of the openfield. The number of squares crossed with all four paws were scored for 5 min (Haleem et al., 1994a). In the similar manner a test drug injected rat was also observed for openfield activity.

***Statistical Analysis:***

Data was analyzed by Two-way ANOVA. Intergroup comparisons were made by Newman-keuls statistics. p values $< 0.01$ and $<0.05$ were considered as highly significant and significant respectively.

## RESULTS AND DISCUSSION

Neuroleptic and antidepressant drugs affect motor activity, and hypermotility produced by amphetamine and metamphetamine (Bradbury et al., 1983, Baldessarini 1986). Nearly all the neuroleptic agents used in psychiatry diminish spontaneous motor activity in animals as well as in human beings (Baldessarini 1996).

Locomotion is mainly controlled by the DA because it had been observed previously that, neuroleptics which are antagonist to DA receptors decreases locomotion in animals. Stress also affects the locomotion of animals. It had been observed that rats exposed to restraint stress exhibited decreased locomotion and increased defecation in an openfield 24 hours later(Haleem and Perveen 1994b).

Sex differences affect the ambulatory openfield activity of animals as well. It has been reported that female exploratory activity is greater than males (Haleem et al., 1988).

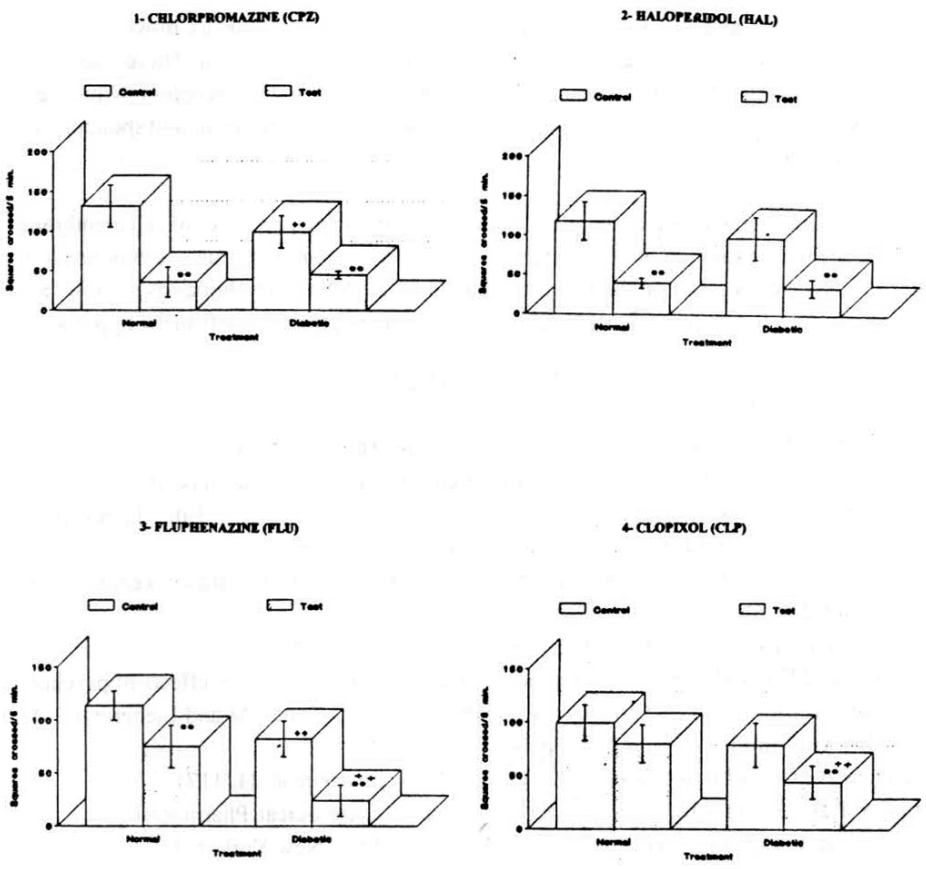
The present work on normal and diabetic animals openfield activity showed that the Chlorpromazine, Haloperidol, and Fluphenazine, had reduced the openfield activity significantly, while Clopixol had insignificantly reduced the openfield activity in normal test animals as compared to normal control animals (Fig. 1-4).

Similarly in diabetic animals the Chlorpromazine, Haloperidol, Fluphenazine and Clopixol had significantly reduced the openfield activity as compared to diabetic controls (Fig. 1-4).

Post-hoc comparison between normal and diabetic test groups showed that the fluphenazine and clopixol had reduced the openfield activity of diabetic animals more significantly ($p < 0.01$), than in normal test animals. In case of CPZ and haloperidol treated animals no significant difference was noted between normal and diabetic test animals.

Among control groups both normal and diabetic, the diabetic controls of all drugs showed reduced activity as compared to normal animals. In diabetic controls of Chlorpromazine and Fluphenazine the reduction in activity was highly significant. This reduction of openfield activity in diabetic control animals could be due to stress as previous studies have shown that stress decreases locomotion in rats (Stone et al., 1995). The animals might be under stress because of their diseased diabetic state, or this reduction in activity could be due to changes in DA turnover. It was noted earlier that the ambulatory activity of STZ-induced diabetic rats was affected by fluctuations in DA turnover (Shimomura et al., 1990).

The effects of these drugs are consistent with the previous observations considering the openfield activity of animals. It had been noted previously that CPZ cause an overall reduction in motor activity and a state of unresponsiveness and indifference, characterized by a loss of interest in the environment and in food, but without marked sedation and with




Openfield activity after treatment with antipsychotics in normal and hyperglycemic rats. Values are mean + S.D. (n=6). Significant differences by Newman- keuls test *$p < 0.05$, **$p < 0.01$ as compared to saline injected rats, $^{+}p < 0.05$, $^{++}p < 0.01$ as compared to normal rats following Two-Way ANOVA df (1,20).

1-F(CPZ) = 91.7 ($p < 0.01$), F(diabetes) = 2.18 (p = NS), F (interaction) = 7.0 ( $p < 0.05$)

2-F(HLP) = 79.44 ($p < 0.01$), F (diabetes) = 2.55 (p = NS), F(interaction) = 0.9 (p = NS).

3-F(FLU) = 56.84 ($p < 0.01$), F (diabetes)= 41.3 ( $p < 0.01$), F (interaction) = 2.2 (p = NS).

4-F(CLP) = 13.84 ($p < 0.01$), F(diabetes) = 14.8 ($p < 0.01$), F(interaction) = 1.0 (p=NS).

full retention of muscular power (Bradley, 1963).

Haloperidol and SCH23390, a sedative and DA D-1 receptor antagonist was found to reduce the spontaneous locomotor activity significantly in diabetic mice (Junzo et al., 1994).

Fluphenazine also suppresses complex behaviour and spontaneous movements but leaves untouched spinal reflexes and unconditioned nociceptive behaviour. These effects are due to the blocking action of fluphenazine at the postsynaptic DA-D-2 receptors (Nimegeers and Janssen, 1979). Similarly Clopixol also suppresses complex behaviour and spontaneous movements (Dollery, 1991c).

In conclusion it seems that changes do occur in transporting properties of cell membrane and endogenous insulin do play an important role in the transport of drugs. It may result in either increase or decrease in the pharmacological effects of antipsychotics as seen in case of fluphenazine and clopixol. Further detailed studies are required to confirm the hypothesis.

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