Effect of Some Psychoactive Drugs on Stress Induced Alteration in Plasma Corticosterone Level

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Abstract

Psychoactive drugs such as chiorpromazine, fluphenazine, haloperidol, propranolol and diazepam were evaluated fortheirability to block stress induced changes in Wistaralbino rats. Thestress induced changes were monitored as the difference in plasma corticosterone (PCS) levels, before and after the administration of minimum effective doses of psychoactive drugs. Significant results were obtained with diazepam at the dose of 5- 10 mg/kg and to a lesser extent with propranolol 20 mg/kg. Other drugs, at their minimum effective doses showed no significant change in plasma corticosterone levels (JPMA 45:153, 1995).

Introduction

Stress induced increase inplasmacorticocosterone level and the response of various drugs on it has been reported by various workers[1-3]. This study also used Plasma corticosterone level as a stress marker for measuring anxiolytic activity of some psychoactive drugs like chlorpromazine, fluphenazine, haloperidol, propranolol and diazepam at their effective doses.

Materials and Methods

Male Wistar albino rats weighing 130-150 gm were selected for experiments in a group of five each alongwith the controls. The selected animals were housed/caged overnight in a quiet place and fed as in routine. The following day, each group of animals were injected with effective doses of chropromazine, fluphenazine, haloperidol, pmpranalol and diazeparn and kept in the different marked cages equipped with screen tops alongwith controls. One hour after injection of drugs, a Novel Environment Stiess (NES) was applied. The caged animals were transferred from animal room to the laboratory. In addition to a primary stress, radio was played loudly for 30 minutes and then each group of animals (n=5) were selected and sacrificed by decapitation and immediately exanguinated into hepannized centrifuge tubes. The blood was immediately centrifuged for 10 minutes at 2000 rpm and plasma was removed, quickly frozen and stored at -40°C until assay. Spectoflourmetric method using chemicals of Ana/R grade (E. Merck) was employed for estimating plasma corticosterone level[4]. All data reported as mean±SEM and calculations were made using student “t” test[5].

Results

Results of stress induced changes in control and treated animals are summarized in (Table I-IV).

Table I. Effect of novel environmental stress (NES) on plasma corticosterone (PCS) level in wistar rats (n=5).

Treatment	PCS level µg/100 ml
Control	22.0±2.5
Vehicle + Without NES	22.2±5.1
Vehicle + with NES	50.0+5.6

Table II. Effect of novel environmental stress (NES) on plasma corticosterone level (PCS) as a function of time in wistar rats (n=5).

NES Time (hours)	PCS level µg/100 ml
0.0	14.5±4.9
0.5	80.0±5.0
1.0	102.0±3.4
2.0	15.0±5.7

Table III. Effect of diazepam on plasma corticosterone (PCS) level of stressed wistar rats (n=5).

Dose of Diazepam mg/kg	PCS level µg/100 ml	Probability
0.0	72.0±5.2	-
1.25	60.0±7.2	NS
2.5	50.0±6.5	NS
5.0	27.0±5.1	P<0.01
10.0	22.0±4.3	P<0.01

NS= Non-significant

Table IV. Effect of psychoactive drugs on plasma corticosterone (PCS) level in stressed wistar rats (n=5).

Dose of drugs mg/kg	PCS level (mg/100 ml) No Drug + NES	Drug + NES
Chlorpromazine (10 mg/kg)	118.0±2.5	116.0±1.7
Haloperidol (25 mg/kg)	115.4±3.8	115.0±2.1
Fluphenazine (0.1 mg/kg)	115.1±1.2	114.0±3.2
Propranolol (20 mg/kg)	103.0±4.0	80.0±2.2
Propranolol (25 mg/kg)	110.2±2.1	86.0±1.5

These results are mentioned as change in plasma corticosterone (PCS) level. Maximum basal level of PCS (22 mg/ml in control rats and in rats with vehicle without applying NES (22.2 mg/100 ml) was nearly same, wheras PCS level increases after applying NES to 50 mg/l00 ml (Table I). Effect of NES as a function of time is also summarized in (Table II). Initially there was no change but after 0.5 hour the PCS level started to increase and reached to a maximum at 1 hour. While after 2 hours PCS level returned nearly to normal showing that stress was over. PCS levels in drug treated animals showed a dose dependent response with diazepam, exhibiting a significant decrease (P>O.01) in PCS levels at effective doses of 5 and 10 mg/kg (Table III). Propranolol showed a significant decrease (P<0.01)inPCS level at minimum effective dose of 20 mg/kg (Table IV). When the dose was increased by 5 mg/kg (25 mg/kg) there was no further decrease in the PCS level. Other psychoactive drugs (chiorpromazine, haloperidol and fluphenazine) were found ineffective when their respective effective doses were administered i.e. 10 mg/kg, 25 mg/kgand 0.1 mg/kg (Table IV).

Discussion

Plasma corticosterone level changes in stressful situations and is therefore, used as stress marker[1,6]. Our results show that under rigidly controlled conditions of mild stress, generally those drugs having anxiolytic activity are effective in antagonizing the elevation of PCS level. The results with diazepam are significant and are in accordance with those of some psychoactive drugs reported earlier[7,8]. Propranolol showedadecrease inthe PCS level with its minimumeffective dose, whereas chiorpromazine, fluphenazine and haloperidol showed no effect on PCS level which is completely different from psychoactive drugs7,8.

The comparison of the structure and line of action of diazepain with other drugs used in the experiment, suggests that this difference of behaviour may be due to the structure of diazepam which is different from other psychoactive drugs (Figure).

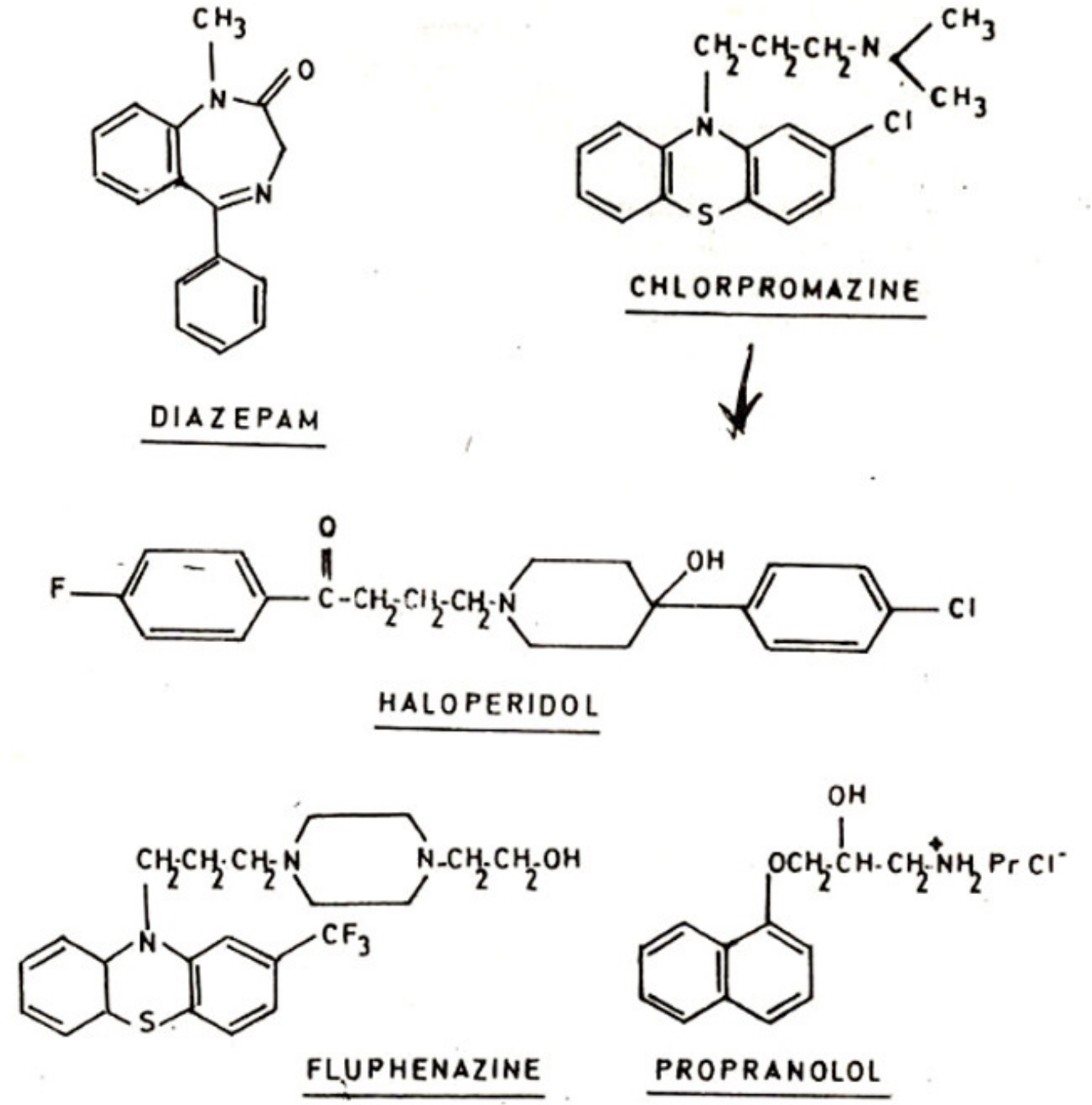

Figure. Structure of psychoactive drugs studied.

Diazepam is a benzodiazepine i.e., a seven member ring containing two nitrogens sandwiched between two aromatic rings. It acts through the gamma amino butyric acid (GABA) receptors which are functionally linked with two sub-types (GABA-A) and (GABA-B) receptors and together these receptors regulate the opening and closing of chloride ion channels. These receptors with diazepam enhance the capacity of each other to open the chloride channel and hyperpolarize the postsynaptic cell[9]. Chiorpromazine is a phenothiazine derivative, Fluphenazine is a thioxanthine derivative, while haloperidol is a butyrophenone derivative. These drugs are known to act on dopamine receptors inhibiting amphetamine induced hypermotiity, stero-typed behaviour suppression of conditioned

avoidance response and production of catalepsy[10]. The degree of blockade persisted for many hours after drugs were stopped due to prevailing plasma concentration, no such blockade was demonstrated in other tricyclic antidepressants[11]. Propranolol is a b-blocker, used as antihypersensitive and antianginal agent, gained reputation as good stress-releasing agent. Our results showed that it has some reducing effect on PCS level at the minimum effective dose which suggests that propranolol has some anti-stress propeflies. Normally b-blocker, activate the hormones sensitive to lipase leading to the release of fatty acids into circulation which may elevate triglycerides and decrease HDL levels but causing no change in LDL[12]. An elevation in adrenaline concentration is also associated with stress causing hypocalcemia[13]. Adrenaline and other factors may contribute to stress therefore, propranolol imparts some significant effect on PCS level at the minimum effective dose.

On the basis of our results it may be concluded that propranolol has some anti-stress property whereas, diazepam is a good antistress drug and compounds of similar skeleton might be useful as stress releasing agents. This work will fuitherbe extended to see the effect of stress on 5Ht, histamine and leukotrienes.

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