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EFFECTS OF DIAZEPAM AND CINCHOCAINE ON BIOGENIC AMINES

SYEDA AFROZ, SHAHIDA P. AHMED, SAIDA HAIDER* AND DARAKHSHAN J. HALEEM*
Department of Pharmacology, Faculty of Pharmacy
**Department of Biochemistry,*
University of Karachi, Karachi-75270, Pakistan

ABSTRACT

Neurochemical and behavioural research show that benzodiazepines are well know anxiolytic drugs which am also used for the treatment of epilepsy, hypnosis and insomnia. Administration of benzodiazepine to experimental animals produces anxiolytic-like effects in various animals and decreases exploratory activity. Psychomotor stimulants such as cinchocaine also showed potent effect on brain biogenic amines and their metabolite. The present studies indicate the changes in dopamine and 5-HT and their metabolites levels after acute administration of cinchocaine and diazepam.

INTRODUCTION

Several classes of drugs are effective in the symptomatic treatment of psychosis. Antipsychotics are mostly used in the therapy of schizophrenia, organic psychoses, the manic phase of manic depressive illness and other acute idiopathic psychotic illness and other acute diseases. Their occasional use may be indicated in depression or in serve anxiety. The use of antipsychotic agents is widespread while the antipsychotic drugs have a revolutionary beneficial impact on medical and psychiatric practice. Association of these agents with extrapyramidal neurological effects have been discussed by Baldesarine *et al.* (1980). Present study is designed to investigate the effects of diazepam and cinchocaine on biogenic amines.

The biogenic amine theory suggests that depression is due to paucity of dopamine, norepinephrine, serotonin neurotransmission, in the brain whereas mania is caused by excessive moroamine neurotransmission (James, 1994). Dopamine is synthesized from dopa, the hydroxylated congener of the amino acid tyrosine (Goodman and Gillman, 1991; Mary *et al*, 1993).

Studies on models of anxiety led to the suggestion that central serotonin (5-HT) system is involved in response to aversive events (Cook and Sepinwall, 1973; Stein *et al.,*

1977) and that the anxiolytic effects of drugs such as benzodiazepine resulted from a reduction in the activities of serotonin system (Stein *et al,* 1973).

It has been suggested on the basis of previous behavioural and neurochemical studies that 5-HT could be considered as a central neurotransmitter involved in the modulation of anxiety and antianxiety effects of benmdiazepine (Apter and Greenberg, 1994). The advent of selective agonists and antagonists for MIT receptor subtypes has rekindled investigation for the role of 5-HT in anxiety mechanisms (Eison and Eison, 1994) one of the pro-posed mechanisms of action for the anxiolytic effects of the benmdiazepine is via a de-crease in central serotonergic neurotransmission (Wright *et al,* 1992). Experimental evidences suggest that overactivity of serotonergic pathways may contribute to the production of pathological anxiety (Andrew and Edd, 1993). Cocaine is a powerful psychomotor stimulant that activates locomotor and stereotype behaviours in rats. Cocaine induced behaviour is thought to be mediated via its actions as an indirect dopaminergic agonist (Gropetti *et al*, 1973; Cheraj, 1993). The behavioural effects of repeated cocaine administration may involve changes at the levels of presynaptic and postsynaptic receptors functions (Nesller, 1992; White *et al.,* 1993). Acute effects of a single dose of cocaine and residual effects of chronic cocaine treatment are distinctly different and occur in different regions of the brain (Orzi *et al.,* 1995).

The present paper deals with the effects of acute administration of cinchocaine (cocaine analogue) and diazepam in mice.

MATERIAL AND METHODS

In present study 6 mice of +NMRI strain (n=6) were used. Animals were obtained from PCSIR Laboratories, Karachi.

Animals were acclimatized for a period of 5 days and maintained under controlled conditions of normal humidity and temperature with standard altering periods of light and darkness before initiating any experimental procedure. Food and water were provided ad libitum. The group of mice were sacrificed by decapitation 40 minutes after drug administration. The whole brain was removed immediately on an ice plate and weight of individual brain was noted and allowed to freeze at -70°C. HPLC with EC detector was used for the estimation of brain biogenic amines concentrations (Haleem *et al,* 1989, 1990; Haleem, 1992).

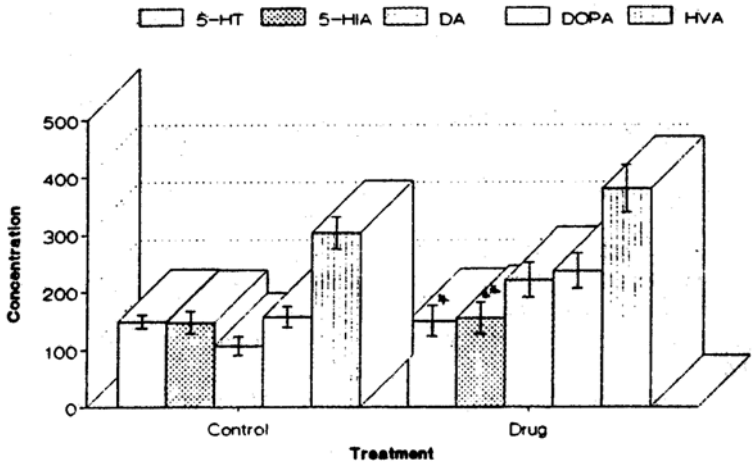
RESULTS AND DISCUSSION

In conclusion present study suggests that systemically administered diazepam increases brain tryptophan levels. Diazepam induced changes of brain regional 5-HT levels and metabolism are explainable in terms of (1) as increase in the availability of

tryptophan to the brain possibly due to an increase of plasma free tryptophan levels. (2) inhibition of serotonin release manifested by the facilitation of GABAergic neurotransmission and (3) interaction of benzodiazepines and/or 5-HT with other neurotransmitters. Evidence suggest that inhibitory effects on diazepam on 5-HT are anxiolytic (Handley and McBlane, 1993). Changes of 5-HT metabolism in other brain regions may well be involved in neuroendocrine, anorectic and psychomotor effects of diazepam. The present contribution also focusses that administration of diazepam resulted in depression of spotnaneous loco-motor activity in a novel as well as familiar environment due to sedation.

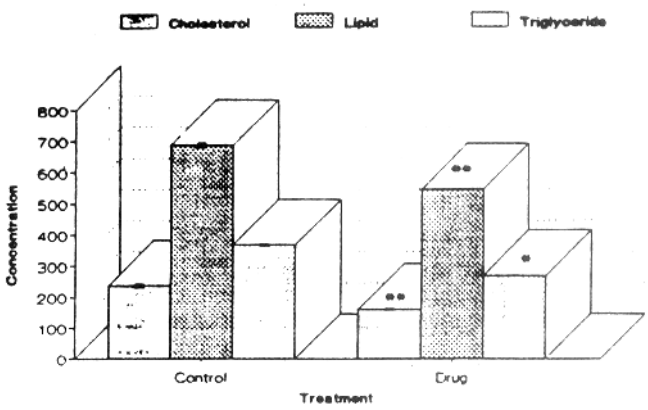
Cocaine inhibit reuptake of amines but are restricted in their releasing proportion. Cocaine appears to effect vesicular pools of dopamine (Ritz and Kuhar, 1989). Cocaine is active on amine release from severe terminals involves inputs flow dependent release of vesicularly), stored transmitters requiring electrical activity and the presence of Ca^{++} (Carboni *et al,* 1989; Hurd and Ungerstedt, 1989).

Cinchocaine is also a cocaine-like drug and effects of cinchocaine arc expected to be similar. Inhibitory effects at uptake sites for monoamine neurotransmitter including 5-HT, dopamine and norepinephrine (Ritz and Kuhar, 1989). Our results suggests that acute ad-ministration of cinchocaine causes a significant increase in monoamine and their metabolites are significantly increased (P=0.05 and P=0.0l). Difference between amines concentration of cinchocaine treated group and control group are obtained and analyzed by one-way ANOVA.



Effect of drug on dopamine, DOPACHVA, 5-HT and 5-HIAA.
Values represented are mean ± S.D. (N). Significant differences by Newmankeuls test.
**P<<0.01 from control.

Present article suggests that cinchocaine is not only a potent reuptake inhibitor of monoamines as cocaine but it also increases the release of monoamine by indirect action on vesicles by increasing the release of neurotransmitter.



Effect of neuroleptic drug on cholesterol, lipid and triglycerides level in control and test animals.
Post-hoc analysis by Student t-test (*P<0.05, **P<0.01)

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