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EFFECTS OF CINCHOCAINE COCAINE ANALOGS ON BRAIN MONO AMINES AND THEIR METABOLITES IN MALE MICE.

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ABSTRACT:

Cinchocaine analogs were studied to determine the effects of acute administration of cocaine analogs on dopamine, 5-hydroxytryptamine (5-HT) and their metabolites. Psychomotor stimulants, (such as cinchocaine), potently influencing dopamine transport carrier were used to characterize in-vivo DA transmission. DA, DOPAC, HVA level and indoleamine were measured in brain after drug administration. Significant changes in levels of DA, DOPAC, 5-HT, SHIAA and HVA were noted. The present findings suggests that acute administration of cinchocaine increases the level of Dopamine, 5-HT and their metabolites and alter the level of amines as compare to control group. These studies also indicate that difference in structure do not affect the binding sites and inhibition of amine uptake.

INTRODUCTION

Thousands of signals race through our brain each moment, controlling our breathing movements, thoughts and emotions with admirable precision. Neuronal cirucits provide basic "Road Map" for brain signals, and chemical neurotransmitters *car*r*y* information from one neuron to another. Neurotransmission in the brain parallels that in the autonomic nervous system, but utilizes several chemicals and peptides in addition to acetylcholine and nor-epinephrine.

The biogenic amine theory suggests that depression is due to paucity of dopamine, nor-epinephrine, serotonin neurotransmission, in the brain, whereas mania is caused by excessive monoamine neurotransmission (James, M.O. 1994). Dopamine is synthesized from dopa, the hydroxylated congener of the amino acid tyrosine (Goodman's and Gilman's, 1991, Mary *et al*., 1993). Dopamine receptors are classified as Dl and D2 receptors. Activation either subtype inhibits the rate of

neuronal firing (Bunzow, *et al.,* 1988, Chido and Bunney, 1987, Seeman and Niznik, 1988). Particularly important dopaminergic pathways include:

i) The nigrostriatal pathway (from substantia nigra to striatum).
ii) Neurons of the chemoreceptor trigger zone of the medulla, which controls vomiting.
iii) Projections from the hypothalamus to the intermediate lobe of the pituitary which are thought to regulate prolactin release.

Antipsychotic drugs inhibits dopamine stimulated adenylate cyclase (usually associated with DI receptor) suggesting that psychoses may result from overstimulation of dopamine receptors (Bjorklund and Lindvall, 1986, Hokfelt, *et al.,* 1978). Dopamine is taken up into the neuron, and not bounding to the storage granules, is metabolized by monoamine-oxidase (MAO) enzyme is located mostly on mitochondria, and by catechol-o-methyl transfersase (COMT). The major metabolites formed in dopamine are 3,4 dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) (Kruk and Pycok, 1991).

The aminoacid tryptophan is hydroxylated then decarboxylated to form 5-hydroxy tryptamine (5-HT). 5-HT is released from inhibitory neurons that originates in the raphe nuclei of the pons and mid brain. 5-HT stimulates either 5-HT1 or 5-HT2 receptors (Goodman's and Gilman's, 1991). 5-HT not bound into storage vesicles will be converted into inactive metabolite by the enzyme monoamine oxidise (MAO) enzyme oxidatively deaminates 5-HT into 5-Hydroxyindole. acetaldehyde further degraded by aldehyde dehydrogenase into 5-Hydroxyindole acetic acid (5-HIAA), the major inactive metabolite of 5-HT (Kruk and Pycock, 1991).

Cocaine is a powerful psychomotor stimulant that activates locomotor and stereotypic behavior in rats. Cocaine induced behavior is thought to be mediated via its actions as an indirect dopaminergic agonist (Gropetti *et al.,* 1973, Chen, J., 1993). The behavioral effects of repeated cocaine administration may involve changes at the levels of presynaptic and postsynaptic receptors function, (White *et at,* 1993, Nestler, E.J., 1992). 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).

Chronic cocaine administration results in compensatory mechanism of the dopamine system such as decrease dopamine synthesis (Trulson and Ulisey, 1987,

Maisonneuve and Kreek, 1995, Giros and Caron, 1993). In present study we use cinchocaine (Cocaine related drug) exclusively for spinal analgesia with perineal analgesia, no fall in blood pressure, and therefore no ephedrine is needed.

The present experiment addresses the issue of effects of acute cinchocaine treatments in mice, and studies the brain dopamine and 5-HT release and metabolism in-vivo.

MATERIAL AND METHOD

In present study 10 male mice of +NMRI strain (n=10) in control group and 6 male mice of +NMRI strain (n=6) in drug treated group were used. Animals were obtained from Agha Khan Medical University.

Male mice of +NMRI (Probably 20 gm) acclimatized for a period of 5 days and maintained under controlled conditions of normal humidity and temperature with standard alternating 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 iceplate 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 concentration (Haleem, D.1., 1992, Haleem, D.1. *et al.,* 1989, Haleem, D.J. *et al.,* 1990).

RESULTS AND DISCUSSION

Although pharmacological properties of cocaine have been widely studied, little is known about its mechanism of action in-vivo. It appears that cocaine exerts its neural action through prolonging the activity of dopamine and serotonin. In the present study the effects of cocaine related drug were evaluated for their pharmacological profile. The theme of the study is to evaluate the effect of drug on brain biogenic amines especially dopamine, 5-HT and their metabolites.

Cocaine inhibit reuptake of amines but are restricted in their releasing properties. Cocaine appears to affect vesicular pools of dopamine (Ritz and Kuhar, 1989). Cocaine's action on amine release from nerve terminals involves impulse-flow dependent release of vesicularly stored transmitters requiring electrial activity and

the presence of Ca++ (Carboni, et al., 1989, Hurd and Ungerstedt, 1989a).

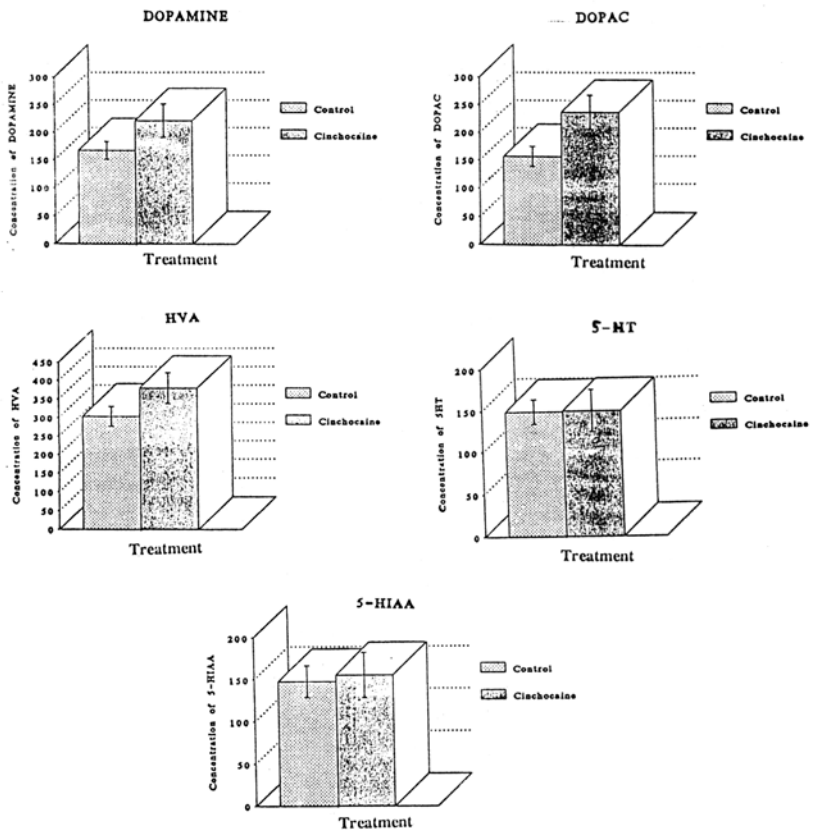

Fig. 1: Effect of Cinchocaine on Dopamine, DOPAC, HVA, 5-HT and 5-HIAA. Values represented are mean ± S.D. (n=6). Significant differences by Newman-Keuls test *p<0.05, **<0.01 from control following 1-way ANOVA.

Cocaine has well known inhibitory effects at uptake sites for monoamine neurotransmitter including 5-HT, dopamine and nor-epinephrine (Ritz and Kuhar, 1989). Our results suggests that acute administration of cinhocaine causes a significant increase in monoamine and their metabolites concentrations. Statistically these results shows that concentration of monoamine and their metabolites are significantly increased P=0.05 and P=0.01 Difference between amines concentration of cinchocaine treated group and control group are obtained and analyzed by one way ANOVA.

Present study suggests that cinchocaine is not only a potent re-uptake inhibitor of monoamines as cocaine, but it also increases the release of monoamine by indirect action on vesicles by increasing the release of neurotransmitter. This is a preliminary study and requires research on its exact mode of action and possible therapeutic uses.

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