Effects of prenatal cocaine exposure on the developing rat:Pharmacological and neurobehavioral studies

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Cocaine is a powerful reinforcer that has become a popular drug of abuse in man. CNS effects that are related to the abuse of cocaine include feeling of well-being and euphoria. Brain dopamine systems are thought to mediate reinforcement and it is often assumed that cocaine's inhibition of dopamine uptake is the mechanism underlying its reinforcing effects.

With increase in cocaine use among general population in recent years, adverse effects of the drug have occurred in all social strata and age groups. Therefore, it has been recegnized that the epidemic of cocaine abuse is a growing major concerning public health.

One of the most troubling aspects of cocaine abuse is its use by pregnant women. Drug abuse during pregnancy puts two lives at risk. Cocaine produces toxic effects on the fetus at concerntrations that are apparently nontoxic to the mother. Not only does cocaine cross the placenta via diffusion and via rapid penetration to mucous membranes, due to its high lipid solubility, but cocaine can also be found in breast milk, the effects of the cocaine can persist long after the child is born. Although it is known that prenatal cocaine exposure is associated with developmental risk to the fetus and newborn, few studies have been conducted to assess the mechanisms whereby either short-term or long-term administration of cocaine can exert its harmful effects on the mother or the child. Therefore, it was our great interest to investigate the pharmacological and neurobehavioral changes in offspring that are prenatally exposed to cocaine.

The present investigation was conducted in an attempt to clearly understand the full extent of the neurobehavioral changes of prenatal cocaine-exposed offspring and the involvement of dopaminergic system related to those changes if there are changes. To achieve this goal, study was approached into three categories following 1) neurobehavioral study, 2) study of dopamine receptor pharmacology, and 3) study of biochemical pharmacology.

The experiments outlined here were performed on female pregnant Sprague-Dawley rats and their offspring. Time-pregnant female rats at gestation day 7(GD7)were adopted to a 12 hr light:12 hr dark illumination cycle were used in this study. Cocaine HCl (40 mg/kg in saline, s.c.) was administered into each dam from GD12 to GD21. Control dams were injected with 0.9% saline. On GD22, dams were allowed to deliver and nurse their own young. Pups were weaned at PND21.

According to present study, there was no significant difference in maternal body weight during gestation and postnatal offspring growth in cocaine-treated group compared to saline-control group. However, a delay in female sexual puberty was noticed in cocaine exposed offspring.

For the behavioral study, motor activity & ataxia, latent learning test (water maze), cold water swimming test and straining cage stress test were applied. The

present study revealed there was no significant difference in offspring's behavior toward motor activity and ataxia between prenatal cocaine-treated group and saline-control group. However, in the water maze, prenatal cocaine treated male offspring showed significant delay in latency time which implying lack of learning ability, while female offspring did not show any significant difference in between the two groups. Male and female offspring showed significantly less endurance in swimming test compared to control offspring. In the immobilization study, prenatal cocaine exposure offspring resulted in significant increase in corticosterone level while saline-control offspring showed returning to basal level of corticosterone as immobilization continued.

There was a decreased in binding affinity to transporter protein on striatum of prenatal cocaine-exposed male offspring and there was no significant changes in hippocampus and hypothalamus. D2 receptor binding study indicated that there was an increased in binding afffinity of prenatal cocaine-exposed offspring brain tissue, striatum with unchanged Bmax. No significant differences were found in the nucleus accumbens between the two groups. D1 receptor binding study revealed that both Kd and Bmax were not significantly different between the prenatal cocaine-treated brain tissue to those of prenatal saline-control.

According to *in vitro* dopamine uptake study, it was found that striatal and nucleus accumbens tissue slices showed a left-shift of dose response curve in inhibitiion of [^{3}H] DA uptake in prenatal cocaine-treated offspring's brain(PND30). The result indicated that there sould be more available dopamine in the synapse which stimulate dopaminergic innervatiion strongly than prenatal saline-control group. However, *in vitro* dopamine release study revealed that an increase in dopamine release of prenatal cocaine-exposed offspring's brain tissue was not greater than those of saline-control.

Based on the present study, it was concluded that prenatal cocaine exposure induce changes the DA transporter binding which may affect on DA uptake and DA release and this alteration may also changes in D2 receptor binding affinity. These alterations in dopaminergic system would result in neurobehavioral changes in offspring. Therefore, it is clear that prenatal cocaine exposure will prolong its undesired effect on dopaminergic system in the prenatal cocaine exposure will prolong its undesired effect on dopaminergic system in the prenatally cocaine exposed offspring's brain consequently altering offspring's behaviors until PND60