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Pharmacology Biochemistry and Behavior, Vol. 55, No. 4, pp. 585–593, 1996

0091-3057/96 $15.00 + .00

PII S0091-3057(96)00280-8

Monoamine Transporters and the Neurobehavioral Teratology of Cocaine

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Received 4 April 1996; Revised 10 June 1996; Accepted 11 June 1996

MEYER, J. S., L. P. SHEARMAN AND L. M. COLLINS. *Monoamine transporters and the neurobehavioral teratology of cocaine.* PHARMACOL BIOCHEM BEHAV **55**(4) 585–593, 1996.—Prenatal cocaine exposure has been associated with various postnatal behavioral abnormalities in human infants, and also with changes in locomotor activity, learning deficits, and altered responses to drug challenge in nonhuman offspring. Several studies have further demonstrated that cocaine exerts an activating effect on fetal behavior. A variety of mechanisms have been proposed to account for the neurobehavioral teratogenic effects of developmental cocaine treatment, including inhibition of fetal brain neurotransmitter uptake and fetal hypoxemia secondary to constriction of the uteroplacental vascular bed. In support of the hypothesis that cocaine effects may be mediated partly by monoamine uptake inhibition, we and other investigators have recently demonstrated the presence of functional dopamine (DA), serotonin (5-HT), and norepinephrine (NE) transporters in the fetal rat brain. Transporter-related cocaine recognition sites are found in a number of fetal brain areas and could mediate the acute effects of cocaine on these areas as well as developmental changes that are manifested postnatally. For example, DA transporter blockade may underlie the above-mentioned activational effects of cocaine on fetal behavior. Time-dependent changes in DA or 5-HT transporter expression produced by prenatal cocaine exposure could likewise play an important role in some of the behavioral effects observed when offspring are tested postnatally.

Prenatal Development Dopamine Serotonin Norepinephrine Uptake

SINCE the first report appeared over 10 years ago describing the behavior of cocaine-exposed neonates (15), much research has been devoted to this topic. Nevertheless, many questions remain unanswered at the present time. For example, the potency of cocaine as a neurobehavioral teratogen remains a matter of contention among many investigators. Furthermore, even if cocaine does exert a detrimental influence on development, the underlying mechanisms are not yet known. In this paper, we first selectively review some of the major effects of in utero cocaine exposure in humans and experimental animals. This is followed by a consideration of fetal brain and placental monoamine transporters as potential targets of prenatal cocaine action based on recent findings from our laboratory and from other investigators. The final section then attempts to relate cocaine-mediated blockade of monoamine uptake to some of the effects of developmental cocaine exposure.

DEVELOPMENTAL EFFECTS OF PRENATAL COCAINE EXPOSURE

Human Studies

Like several other abused substances, cocaine has been reported to exert adverse effects on fetal growth and development. Consequently, cocaine-exposed neonates typically exhibit reductions in mean birth weight and head circumference compared to non-exposed controls (reviewed in 28,90). These differences are partly related to a higher incidence of premature delivery, however even full-term infants may be small for their gestational age. There is also some evidence that prenatal cocaine exposure may increase the risk of certain types of congenital abnormalities, particularly those produced by vascular accidents (42,103). Ultrasonographic techniques permit the noninvasive study of fetal behavioral state under normal conditions as well as in response to perturbations such as maternal drug consumption. Results obtained using this approach suggest an activational effect of acute cocaine exposure on fetal behavior. More specifically, maternal cocaine use was associated with increased fetal movement and startle in a case study of one fetus (36) and with increased movement, sucking behavior, hyperflexion, and irritability in 3 out of 20 fetuses examined in a larger study (43). Inconsistent findings in the latter study could be related to variability in both the amount of cocaine consumed by the mother and the elapsed time between cocaine use (which occurred before arrival at the clinic) and measurement of fetal state.

Most of the postnatal studies of infants exposed to cocaine

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in utero have focused on possible behavioral abnormalities assessed by the Neonatal Behavioral Assessment Scale (NBAS) (9). This test battery evaluates several areas of infant behavior, including sensory orientation, habituation, motor function, presence of abnormal reflexes, range of behavioral state, and regulation of behavioral state. A number of studies have reported behavioral abnormalities in cocaine-exposed neonates on the basis of NBAS testing (reviewed in 28,67). However, the interpretation of these findings is problematic in several ways. First, there has been little consistency in the type of abnormal behavior observed in the cocaine-exposed subjects. Although this could be due to differences in amount and/or pattern of cocaine exposure across studies, it is nonetheless a reason for concern when attempting to identify causal relationships between maternal drug use and offspring behavior. Second, many studies have been methodologically flawed due to the lack of appropriate control groups (28). Cocaine-using women often receive less prenatal care and engage in greater non-cocaine substance use (i.e., polydrug use) than women who do not take cocaine. These factors may be important contributors to the intrauterine growth retardation and behavioral deficits reported for cocaine-exposed infants. Indeed, when maternal drug use is moderate and when investigators more carefully control for potential confounding factors, the results tend to show few or no cocaine-associated deficits on the NBAS (18,76,105). These considerations have led many researchers to conclude that the risks of prenatal cocaine exposure have been overestimated (17,24,29,45,53).

One important limitation of the NBAS is that it fails to assess learning or other cognitive abilities in the subjects. However, several research groups have used other measures to investigate cognitive function in cocaine-exposed children up to several years of age. The results indicate that in utero cocaine exposure is associated with measurable deficits in language development and in IQ (5,77,98). Deficits were even found in cocaine-exposed children who were raised by adoptive parents, thereby excluding the possible adverse effects of rearing by a mother who may still be abusing cocaine (68).

Taken together, the above findings suggest that cocaine probably is a neurobehavioral teratogen in humans. However, the effects produced by prenatal cocaine are likely to vary considerably as a function of the amount and pattern of maternal use, possible (genetic?) differences in fetal vulnerability, and the presence of other risk factors such as polydrug use. Sorting out the contribution of cocaine itself under these conditions has proved to be an extremely difficult problem, which provides an important rationale for controlled animal studies involving developmental cocaine treatment.

Animal Studies

The influence of cocaine administration on fetal behavior or electrocortical activity has been examined in several nonhuman species. A series of studies by Simonik, Robinson, and Smotherman (87–89) showed that intraperitoneal or intracisternal injection of rat fetuses on gestational day (GD) 20 or 21 led to a significant stimulation of motor activity. No such effect was produced by lidocaine, a cocaine-like local anesthetic. Intravenous administration of cocaine to fetal sheep resulted in electrocortical arousal and a reduced percentage of time spent in a state of sleep (1,11). Finally, ovine fetuses injected intravenously with cocaine exhibited increased swallowing, a behavior known to be under monoaminergic control (79). The implication of these findings for understanding cocaine's mechanism of action is discussed below.

Animal studies investigating the influence of maternal cocaine treatment on postnatal offspring behavior have examined several unconditioned behaviors (e.g., locomotor activity, social behaviors), performance on various learning tasks, and behavioral responses to drug challenges. We will briefly discuss some of the work involving activity, learning, and drug-induced behaviors. Vorhees (101) recently reviewed the influence of prenatal cocaine exposure on a variety of learned and unlearned behaviors. The results of studies on activity in cocaine-exposed offspring have been highly variable, with investigators reporting either increased activity, decreased activity, or no change. This variation probably stems at least partly from major differences in experimental design, including differences in maternal treatment regimen, age at which offspring are tested, and the type of apparatus used to measure activity (e.g., photobeam apparatus or open-field).

Spear and her colleagues carried out several studies of learning performance in young offspring of rats injected once-daily with 40 mg/kg of cocaine HCl from GD 8 through GD 20. Compared to controls, the cocaine-exposed pups exhibited deficits in first-order conditioning and sensory preconditioning (37) and in the acquisition of odor preferences reinforced either by milk or cocaine (38,92). Other studies from several laboratories have reported spatial learning deficits in cocaine-exposed rats tested in young adulthood (41,59,91,102). These findings show that in utero cocaine exposure in rats can impair subsequent learning of various tasks. Nevertheless, the behavioral deficits were rather subtle in some cases, and in other studies no significant prenatal drug effects were found (48,78). Therefore, more information needs to be gathered to determine the treatment and test conditions necessary for demonstrating prenatal cocaine-associated learning deficits. Other studies have investigated whether the sensitivity to various pharmacological agents has been altered in the offspring of cocaine-treated subjects. Rats and mice exposed to cocaine prenatally exhibited a subsequent reduction in their sensitivity to cocaine in most (12,39,40,65) but not all (27,70) test situations. Experiments on young animals (pups or weanlings) have also found increased behavioral sensitivity to the dopamine (DA) D_2/D_3 receptor agonist quinpirole (66), decreased sensitivity to the DA receptor antagonist haloperidol (63,92), and increased sensitivity to morphine and the μ-opiate receptor agonist D-Ala^2-NMe-Phe^4-Gly-ol (DAMGO) (33). These studies thus provide functional evidence for prenatal cocaine-induced alterations in the DA and opiate systems.

MECHANISMS OF PRENATAL COCAINE ACTION: FOCUS ON MONOAMINE TRANSPORTERS

As recently reviewed by Olsen (69), a variety of mechanisms may contribute to cocaine-induced developmental neurotoxicity. These include (but are not limited to) interactions with plasma membrane monoamine transporters, fetal and maternal vasoconstriction, increased oxygen radical formation produced by ischemia-reperfusion, alterations in gene expression and neurotrophic activity, calcium ion chelation, and blockade of sodium channels at high cocaine concentrations. In our studies of developmental cocaine effects, we have hypothesized that one important aspect of cocaine action involves its binding to fetal brain and placental monoamine transporters and the consequent inhibition of DA, serotonin (5-HT), and norepinephrine (NE) uptake. This hypothesis is based on the following considerations: (1) because cocaine has a higher affinity for monoamine transporters than for other molecular targets (e.g., sodium channels, muscarinic receptors,

or 5-HT_3 receptors), it mainly affects the transporters at low-to-moderate doses (see 83); (2) inhibition of monoamine (particularly DA and 5-HT) uptake mediates many of the behavioral and physiological effects of cocaine in adult organisms (106); (3) neurotransmitters such as DA and 5-HT have been shown to influence cell growth, migration, and differentiation (54), suggesting that disruption of these transmitters might alter subsequent developmental trajectories; and (4) offspring exposed to cocaine in utero exhibit a variety of changes in monoamine system structure and function (see discussions in 19,83). Therefore, the following sections will review recent studies concerning the normal development of monoamine transporters and the influence of maternal cocaine treatment on these transporters.

Development and Characteristics of Fetal Brain Monoamine Transporters

Plasma membrane transporters mediate the sodium-dependent uptake of various neurotransmitters from the extracellular space (34). Specific transport proteins have been identified for DA, 5-HT, NE, and several amino acid transmitters (4). Because of the potential role of monoamines in both normal and abnormal development, researchers have recently begun to investigate the characteristics of monoamine transporters in fetal brain. Molecular biological approaches have been particularly useful in ascertaining when the expression of transporter genes can first be detected developmentally. Thus, in situ hybridization revealed the presence of DA transporter mRNA in rat brain as early as GD 14 (31,97). This corresponds closely to the time when dopaminergic (tyrosine hydroxylase-positive) fibers first reach the developing striatum (100). 5-HT transporter mRNA has been found in the neural tube of the rat embryo at E (embryonic day) 11, in the raphe nuclei at E 15, and in the caudate at E 21 (35). To our knowledge, no studies have yet been published regarding the ontogeny of NE transporter gene expression in the brain.

Other experiments have demonstrated functional monoamine uptake in the fetal brain (21,46,47,55,64) and have shown that adult and fetal brain transporters respond similarly to monoamine reuptake inhibitors. For example, the pharmacological selectivity of the DA transporter in cultured mesencephalic cells from embryonic (GD 15) rats is comparable to that of the adult DA transporter (10). Furthermore, DA and 5-HT uptake mechanisms in the striatum and frontal cortex of GD 20 rats show similar characteristics to the uptake systems found in the mature brain (46). These findings indicate that cocaine probably exerts uptake- blocking effects during prenatal development, just as it does in adulthood.

Cocaine recognition sites on the monoamine transporters apparently overlap with but are not identical to the sites labeled by drugs that differ structurally from cocaine (6,73,80). Consequently, fetal neurons can only respond directly to cocaine if the developing transporters possess these recognition sites. To address this question, we initially used radioreceptor binding assays with [^{3}H]cocaine to determine whether cocaine binding sites are present in the fetal brain and to investigate their normal development. This approach also provided an overall index of monoamine transporter density, since cocaine binds to all of the monoamine (DA, 5-HT, and NE) transporters. The results showed that [^{3}H]cocaine binding sites were present in whole fetal rat brain as early as GD 15 and increased in density across the ages examined (64) (Fig. 1). Saturation analyses performed at GD 20 yielded curvilinear Scatchard plots that were resolved into a high-affinity site with a K_d of approximately 20 nM and a low-affinity site with a K_d in the micromolar range. Drug competition studies with various monoamine uptake inhibitors were also performed to determine which transporters contributed to fetal brain [^{3}H]cocaine binding. Although not conclusive, the results suggested that [^{3}H]cocaine bound mainly to the 5-HT and DA transporters in fetal rat brain (64).

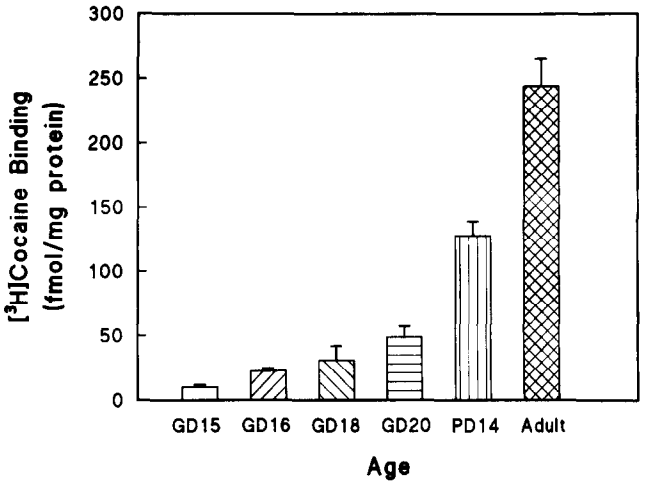

FIG. 1. Normal ontogeny of high-affinity (10 nM) [^{3}H]cocaine binding sites in whole rat-brain membranes. Each point represents the mean ± SEM for either four separate pools of fetal brain tissue (brains from two or more different litters were used for each tissue pool) or six individual PD14 and adult brains. Original data from (64).

More recent experiments in our laboratory have used the potent cocaine congener [^{125}I]RTI-55 to pharmacologically characterize and localize cocaine recognition sites in GD 20 and adult rat brain. Previous studies by other investigators have shown that this ligand selectively labels DA and 5-HT transporters in adult rodent (8,30), monkey (49), and human (60,94) brain using both radioreceptor assays and autoradiographic techniques. As in our previous work with [^{3}H]cocaine, saturation analyses of [^{125}I]RTI-55 binding to whole fetal brain membranes yielded curvilinear Scatchard plots suggestive of multiple binding sites (83). However, the dissociation constants were much lower (mean high-affinity K_d = 0.13 nM, low-affinity K_d = 12 nM), which is consonant with the greater potency of RTI-55 compared to cocaine. Analyses of adult brain [^{125}I]RTI-55 binding yielded somewhat higher K_d values (high-affinity K_d = 0.26 nM, low-affinity K_d = 18 nM), although the difference was statistically significant only for the high-affinity site. Thus, both fetal and adult brain transporters exhibit multiple binding sites for cocaine and cocaine-like drugs, however these sites may undergo some alteration in the course of normal development. Investigators have generally assumed that the high-affinity binding of cocaine and cocaine-like drugs to monoamine transporters is most closely related to the reuptake-blocking properties of these compounds. In contrast, the identity and possible physiological role of low-affinity cocaine binding remains to be determined (see 83 for a discussion of this issue).

Drug competition experiments revealed that the great majority of [^{125}I]RTI-55 binding was to the 5-HT and DA transporters in both fetal and adult brain membranes (83). In vitro autoradiographic studies were also performed to determine the localization of [^{125}I]RTI-55-labeled cocaine recognition

sites. Autoradiograms of fetal brains at the striatal and diencephalic levels showed relatively high levels of [^{125}I]RTI-55 binding in the medial forebrain bundle, septum, cingulate cortex, hippocampus, and lateral habenula, with lower levels of binding in the cortical plate, olfactory tubercle, striatum, and thalamus (83). In almost all brain areas, a low concentration of unlabeled citalopram (a selective 5-HT uptake inhibitor) displaced most of the [^{125}I]RTI-55 binding, indicating that the majority of binding was to the 5-HT transporter. Together with the drug competition studies, this finding suggests that the serotonergic system may be an important target of prenatal cocaine action. Moreover, the demonstration of cocaine recognition sites in various areas of the fetal brain raises the possibility that prenatal cocaine exposure could directly influence the development of neural circuits involved in behavioral functions such as learning and memory (hippocampus and cortex), emotion and motivation (septum), motor control (striatum), and sensory processing (thalamus).

In other recent experiments, we used the selective NE uptake inhibitor nisoxetine to label the NE transporter at different stages of development. [^{3}H]Nisoxetine bound to a single population of sites in GD 20 whole-brain membranes with a mean K_d of 1 nM (84), which is similar to the value reported for adult rat cortex by Tejani-Butt and coworkers (96). Developmental studies found a low level of [^{3}H]nisoxetine binding at GD 15 and a steady increase in binding into adulthood. This timing corresponds closely to the previously mentioned findings concerning the development of rat brain [^{3}H]cocaine binding sites and is also consistent with other studies detailing the time of appearance of DA and 5-HT transporters in fetal brain. Consequently, NE uptake sites in the fetal brain may be an additional target of prenatal cocaine action.

The results described above using radiolabeled cocaine, RTI-55, and other ligands that are more selective for specific transporters have demonstrated the presence of cocaine-sensitive DA, 5-HT, and NE transporters in the fetal rat brain. Extrapolation of these findings to humans suggests that cocaine ingestion by pregnant women could alter offspring neurological and behavioral development in part by blocking fetal monoamine uptake, thereby disturbing subsequent maturation of the monoaminergic systems. To our knowledge, monoamine transporter development has not yet been examined in the human brain. However, a comparison of rats and humans with respect to the timing of monoaminergic cell birth and fiber outgrowth leads to the prediction that human transporter expression may occur at least as early as 9-10 weeks postconception (see 64).

Placental Monoamine Transporters

There has been much speculation that various developmental effects of cocaine may result from restriction of uteroplacental blood flow and consequent fetal hypoxemia. However, research over the past several years has demonstrated the presence of monoamine transporters within the placenta itself, suggesting yet another mechanism by which the fetus could be influenced by maternal cocaine ingestion. One of the first clues to the presence of placental transporters was provided by a report of [^{3}H]cocaine binding sites in human placental villus tissue (2). Other work by Ganapathy and colleagues confirmed the existence of functional 5-HT and NE transporters in human placental brush border membranes (20,75). Moreover, the cloned placental 5-HT transporter was found to be identical in structure to the neuronal and blood platelet 5-HT transporters (74).

To begin developing an animal model of cocaine-placental interactions, we set out to determine whether monoamine transporters can also be detected in the rat placenta. Radioreceptor binding and (in some cases) autoradiographic studies were performed on normal GD 20 placentas using [^{125}I]RTI-55, [^{3}H]nisoxetine, the selective 5-HT transporter ligand [^{3}H]paroxetine, and the selective DA transporter ligand [^{3}H]GBR 12935. Briefly, the results indicated that rat placental membranes possess an extremely high density of NE transporters and a lower but still significant number of 5-HT transporters (85). These transporters do not exhibit the same distribution within the placenta, suggesting that they may be concentrated in different cell types. It is also interesting to note that like the human placenta, the rat placenta does not appear to express specific DA uptake sites.

The roles of monoamine transporters in placental function and fetal development are currently unknown. However, presence of the transporters on brush-border membranes indicates that they are positioned to take up NE and 5-HT from the maternal blood. Ganapathy and coworkers (72,75) have hypothesized that one possible function of these placental uptake systems is to maintain low concentrations of NE and 5-HT in the maternal blood space (the "intervillous space" in human placenta) to minimize potentially harmful vasoactive effects of these transmitters. If this hypothesis is correct, inhibition of placental monoamine uptake by maternal cocaine use could have adverse consequences for normal fetal growth and development.

Regulation of Monoamine Transporters by Cocaine

Understanding the mechanisms of prenatal cocaine action requires not only a delineation of the drug's interactions with the developing brain and placenta, but also a consideration of how these interactions are later manifested as changes in neurotransmitter functioning. Of particular interest is whether repeated cocaine treatment alters subsequent monoamine transporter density or transcriptional regulation. Research on adult animals and humans will be considered first, followed by a review of prenatal cocaine studies.

Because of the important role of DA in cocaine action, researchers have focused on the influence of chronic cocaine exposure on the DA transporter. In many cases, cocaine administration to adult animals has been reported to produce no alterations in striatal [^{3}H]DA uptake or radioligand binding to the DA transporter (reviewed in 108). In those instances where changes have been observed, the effect seems to depend on various factors including (but not limited to) the variable being measured (e.g., in vitro transporter binding, transporter mRNA, or in vivo transporter binding determined by brain imaging), the drug administration regimen, and the temporal relationship between drug administration and transporter measurement. For example, several recent studies found increases in DA transporter binding in rodent brain when analyses were performed within hours to several days following drug treatment (16,52,104). In contrast, withdrawal from cocaine for more than seven days was accompanied by decreased DA transporter binding and reduced levels of DA transporter mRNA (14,52,71,104,107). Studies of DA transporter responses to cocaine in humans have likewise yielded variable results. Both Little et al. (61) and Staley et al. (95) reported increased binding of the cocaine congener [^{3}H]WIN 35,428 to the nucleus accumbens and caudate putamen from cocaine

abusers who had either been using cocaine at their time of death or who had actually died from a cocaine overdose. On the other hand, a similar subject population studied by Hurd and Herkenham (44) showed decreased caudate and putamen DA transporter binding using [^{3}H]mazindol as the ligand. Volkow and coworkers likewise have found evidence for DA transporter down-regulation in cocaine users studied by positron- emission tomography (99). The reason for these conflicting results is unclear at the present time.

The 5-HT transporter is also influenced by cocaine, although the results are again complicated by methodological differences between studies. Thus, increased 5-HT transporter binding was found in the brains of adult rats sacrificed shortly after the cessation of seven days of cocaine treatment (22), whereas fourteen days of cocaine treatment led to a decrease in 5-HT transporter mRNA in the dorsal raphe nucleus (58). Human cocaine/heroin abusers showed increased platelet 5-HT transporter binding (62), but Dackis et al. (23) reported a significant reduction in platelet 5-HT uptake in cocaine abusers compared to control subjects.

To our knowledge, no human studies have yet been performed examining the effects of in utero cocaine exposure on monoamine transporters. However several animal studies have investigated the effects of prenatal cocaine on the binding and/or expression of monoamine transporters postnatally. In one of the few studies to examine DA transporter mRNA expression, de Bartolomeis et al. (25) found no differences between cocaine-exposed and control offspring on postnatal day (PD) 21, which was the only time point examined. On the other hand, membrane binding and autoradiographic studies have reported various effects of prenatal cocaine treatment, although these effects vary depending on the ligand used to label the transporter and the age at which the offspring are examined. Rats whose mothers were given 60 mg/kg/day of cocaine orally from GD 7-21 showed significant decreases in striatal [^{3}H]mazindol binding at postnatal weeks 3 and 4 (93). Injection of pregnant rats with 20 mg/kg/day of cocaine intraperitoneally from GD 10 through parturition resulted in time-dependent changes in striatal [^{3}H]mazindol binding in the offspring (56). Increased binding was observed from PD 1-5, whereas decreases were found on PD 14 and 35. Finally, striatal [^{3}H]WIN 35,428 binding was reduced at 6 weeks postnatal but elevated at 3 and 6 months of age in mice exposed to cocaine prenatally from GD 13-20 (12,51).

We used quantitative in vitro autoradiography with [^{3}H]GBR 12935 to study the influence of prenatal cocaine on postnatal development of the striatal DA transporter (19). One group of pregnant rats was injected subcutaneously (s.c.) from GD 18-21 with either 40 mg/kg/day of cocaine HCl or with saline vehicle. Separate groups of females were implanted s.c. with two Silastic capsules, each containing 60 mg of cocaine base dissolved in polyethylene glycol (PEG) or PEG only, from GD 18-21. Control females were pair-fed to their respective treatment groups. Offspring were fostered to normal lactating dams and were sacrificed for autoradiographic analysis on PD 1, 10, 30, or 60. No differences between treated and control groups were found at any age except for PD 10, where both groups of cocaine-exposed subjects exhibited a substantial down-regulation of DA transporter binding in the dorsal lateral striatum (Fig. 2). Thus, in this study two very different regimens of maternal cocaine administration resulted in virtually identical reductions in striatal DA transporter binding, although the effect was transient in both cases.

There has also been some investigation of prenatal cocaine effects on the 5-HT and NE transporters. Treatment of pregnant rats with 40 mg/kg/day of cocaine from GD 13 through parturition resulted in a 66% decrease in [^{3}H]paroxetine binding to the 5-HT transporter in the cerebral cortex at PD 1 (3). This effect was maintained throughout the first postnatal week at which time a 48% decrease in hippocampal [^{3}H]paroxetine binding was also observed. By four weeks of age, there were no longer any differences between cocaine and control offspring. Likewise, other studies found no effect of prenatal cocaine exposure on hypothalamic or cortical 5-HT uptake sites at either PD 28 (7) or PD 70 (13). With respect to the NE transporter, we recently found that s.c. cocaine implants from GD 17 to GD 20 resulted in a large increase in placental [^{3}H]nisoxetine binding, however no change was observed in the fetal brain (86).

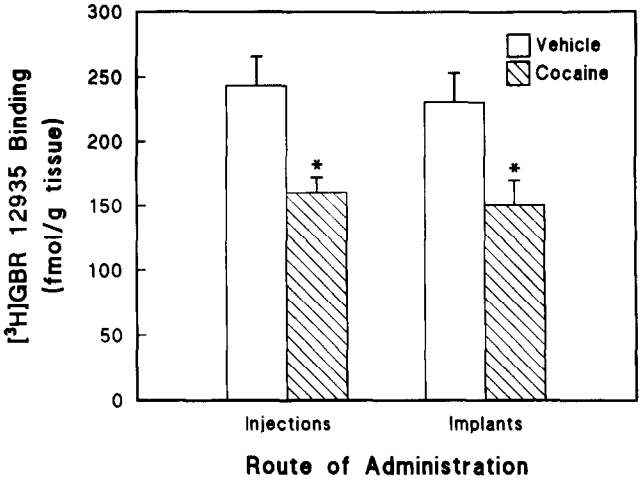

FIG. 2. Effect of prenatal cocaine exposure on [^{3}H]GBR 12935-labeled DA transporters in the dorsal lateral striatum of PD 10 male rats. One group of dams was given daily s.c. injections from GD 8-21 of 40 mg/kg cocaine HCl or saline vehicle. Another group was implanted from GD 18-21 with two s.c. Silastic capsules, each containing 60 mg of cocaine base in polyethylene glycol (PEG) or PEG alone. Control dams were pair-fed to their respective control groups. Offspring were fostered to untreated lactating dams and sacrificed at PD 10 for analysis of DA transporter binding by quantitative in vitro autoradiography. Values shown are the mean ± SEM for 4-6 subjects per group. Only 1 offspring was used from each litter (i.e., litter was the unit of analysis). *$p < 0.05$ compared to the respective control group. Original data from (19).

Studies on DA transporter knockout mice by Giros and colleagues (32) have demonstrated that reuptake plays a critical role in clearing DA from the synaptic cleft following its release. Moreover, knockout mice showed extreme hyperactivity, indicating that chronically elevated synaptic DA levels have important behavioral consequences for the animals. These findings support the hypothesis that the changes in monoamine transporter density discussed above may contribute to some of the behavioral consequences of prenatal cocaine exposure. In particular, altered DA uptake might influence locomotor activity or the behavioral responses to dopaminergic drugs. One such example from our own research is discussed in the concluding section.

CONCLUSIONS

We have seen that cocaine-sensitive monoamine transporters are present in fetal brain and placenta, and also that maternal cocaine treatment can alter offspring and placental trans-

porter binding. The question remains as to whether these findings can help explain the behavioral effects of prenatal cocaine exposure. Due to the multiplicity of mechanisms by which cocaine might alter fetal behavior and subsequent development (69), there unfortunately are no effects that currently can be attributed specifically to cocaine blockade of neurotransmitter uptake. Nevertheless, it is possible to speculate on some possible relationships between transporter blockade and developmental actions of cocaine.

As described earlier, cocaine has been shown to produce behavioral and/or electrophysiological activation in fetal humans, rats, sheep, and pigs. In all of the animal experiments, cocaine was delivered directly to the fetus (intracisternally or intraperitoneally to rats, and intravenously to sheep and pigs), thereby obviating possible drug effects on uteroplacental blood flow. Indeed, measurements of arterial blood pO_2 in the fetal sheep showed no evidence of hypoxemia (1). Since cocaine inhibition of DA uptake in the mesolimbic and nigrostriatal DA pathways is largely responsible for its locomotor stimulating effect in adult animals (106), it is reasonable to hypothesize that a similar process underlies cocaine-induced behavioral activation in the fetus. Moreover, if the consequences of blocking fetal brain reuptake sites differ from the changes that result from maternal vasoconstriction, then such differences could carry over into the postnatal period. This notion is the basis for the hypothesis of Lester et al. (57) that cocaine-exposed human neonates exhibit two distinctive neurobehavioral syndromes: a hyperexcitable syndrome related to direct actions of cocaine on the fetal nervous system, and a depressive syndrome that is secondary to hypoxemia and intrauterine growth retardation.

A second example that may involve the DA transporter concerns the previously mentioned reduction in haloperidol-induced catalepsy in PD 10 rat pups exposed to cocaine prenatally (63). As this experiment used a dose of haloperidol (1 mg/kg) that selectively blocks D_2 receptors in vivo (81), the results could reflect increased striatal D_1 receptor activity (thereby increasing dopaminergic transmission and motoric function). Indeed, two studies have reported increased striatal D_2 receptor binding in young offspring of cocaine-treated dams, however the effects were small (56,82). Therefore, another factor that might be as or more important in altering haloperidol sensitivity at PD 10 is the reduced striatal DA transporter binding we observed in cocaine-exposed pups at the same age (19). If our autoradiographic findings are indicative of decreased DA uptake in vivo, then one would expect heightened synaptic levels of DA and increased overflow. This prediction was borne out in microdialysis studies conducted on prenatal cocaine-exposed and control subjects by Keller and his colleagues (50). Consequently, reduced sensitivity to the behavioral effects of haloperidol could stem not only from postsynaptic receptor changes, but also from enhanced competition for receptor occupancy by DA.

In addition to the findings discussed in this review, many other changes in monoaminergic systems have been reported following prenatal cocaine exposure. The extent to which these changes are due to inhibition of fetal brain and/or placental monoamine uptake is still unclear. One possible approach to this problem is to ascertain whether the effects of maternal cocaine administration on offspring behavior are mimicked by other compounds that selectively block a particular transporter (for example, see 26). This would seem to be a promising approach in theory, however in practice the results may be difficult to interpret due to differences between cocaine and other compounds with respect to transporter binding affinities and clearance rates. Furthermore, some effects of cocaine could be mediated by interactions with more than one transporter. Therefore, elucidating the mechanisms of action of cocaine on fetal development will likely continue to be a daunting problem for researchers interested in the drug's neurobehavioral teratogenic effects.

ACKNOWLEDGEMENT

The research reported in this paper was supported by NIDA grant DA-06495.

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