Comparability of Human and Animal Studies of Developmental Cocaine Exposure

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Human and animal studies of cocaine exposure during development can be compared on many levels and from many different perspectives. The most logical place to begin is to pose the question: What is the best animal model for cocaine abuse during pregnancy, and does the information obtained in a given animal model apply to humans? Of course, due to the complex nature of cocaine's pharmacology, there is no perfect animal model. It is virtually impossible to perfectly model human development in anything other than a human being. Since invasive research is not done in humans, researchers are forced to study an approximation of human development. Each approximation of the human condition, or model, has specific strengths and weaknesses. The data obtained from each model must be evaluated in terms of the strengths and weaknesses of the model.

The major pharmacological actions of cocaine in the maternal-fetal unit include cardiovascular and hemodynamic effects as well as effects on fetal physiology with major targets in the central and peripheral nervous systems. What then are the characteristics that can be ascribed to individuals developmentally exposed to cocaine? Cocaine can affect the individual on many levels: behavioral, cognitive, developmental, and structural. The central nervous system (CNS) receives particular attention in this chapter since cocaine has potent effects on the CNS of the adult.

The biggest hurdle for the animal model is the problem of the polydrug microculture. The influence of lifestyle and, in particular, alcohol and cigarette use, on development including postnatal development is significant. While the effects of alcohol, other drugs, and nicotine can be addressed in animal models, the multidimensional confounds such as socioeconomic status, poor prenatal care, and sexually transmitted disease are difficult to adequately address in animal models. The value of the animal model, or preclinical research, is the ability to determine the biological effects of a substance independent of cultural and sociologic

influences. It is a pure biological system in which the pharmacological and physiological effects of a drug can be studied in detail and quantified.

Historically, specific hypotheses generated through clinical experience and anecdotal evidence are tested in animal models. In the case of cocaine, however, animal studies have, on the whole, been run concurrently with clinical studies. For example, the first animal studies reported teratologic effects of cocaine in the early 1980s (Fantel and MacPhail 1982; Mahalik et al. 1980) and the earliest clinical reports describing structural defects in cocaine-exposed infants were in the mid-1980s (Bingol et al. 1987; Chasnoff et al. 1988; Dixon and Bejar 1989). However, the more recent and carefully controlled animal studies indicate that cocaine is not tera-togenic unless it is administered intraperitoneally (IP).

Webster and colleagues (1991) and Webster and Brown-Woodman (1990) produced digit and CNS malformations when cocaine was administered to the rat IP on gestation day 16. Finnell and colleagues (1990) found that in the mouse, cocaine produced congenital malformations, including cardio-vascular defects, limb abnormalities, and genitourinary malformations when administered IP either during gestation days 6 to 8 or 8 to 10. (The IP route of administration increases the teratogenic potency of drugs due to extraplacental diffusion of the drug to the fetus, resulting in higher drug levels in the fetus than in maternal plasma or tissues (DeVane et al. 1989).)

More recent clinical studies, which include some large retrospective studies such as reviews of birth certificates, also did not find an association between cocaine and structural defects with the possible exception of hydronephrosis (Chavez et al. 1989; Hutchings 1993; Martin et al. 1992; Mehanny et al. 1991). Therefore, as far as structural teratogenesis is concerned, both animal research and clinical studies have found that cocaine is not teratogenic.

In addition to structural alterations, growth of the organism is often used as a measure to determine whether a compound is developmentally toxic. Growth, in general, is the result of multiple influences, including maternal nutrition; uteroplacental blood flow and function; a variety of peripheral receptors in the developing organism; and the function of the maternal and fetal hypothalamic-pituitary axes (HPA) which regulate growth, including growth hormone releasing hormone (GHRH),

somatostatin, growth hormone (GH), and thyroid hormone. Recently, prenatal cocaine exposure has been shown to increase somatostatin levels in forebrain and olfactory bulb following prenatal and/or postnatal exposure (Rodriguez-Sanchez et al. 1991). Whether somatostatin levels in various brain regions correlate with hypothalamic levels was not addressed in the report. However, if they are, in fact, related, one could speculate that since somatostatin inhibits somatic growth, the increased somatostatin levels in fetal brain may be responsible for the reduced body size.

Clinically, a decrease in birthweight is often found in cocaine-exposed neonates. Some authors have described altered patterns of growth, with the head being most affected, while others have found no alteration in body proportionality (Frank et al. 1990; Little and Snell 1991; Mitchell et al. 1988). Generally, in the rat, prenatal cocaine does not reduce birth-weight or alter postnatal growth patterns unless it is administered at toxic levels (Church et al. 1990). However, to the author's knowledge, the proportionality of growth in exposed pups has not been determined. Since animal studies do not show altered birthweights following all but the most toxic doses of cocaine, the decreases in body weights often cited in human studies are most likely caused by factors other than cocaine, such as polydrug, alcohol, and cigarette use.

Both the teratologic effects and the growth effects are generally attributed to cocaine’s effects on the cardiovascular system. Cocaine has potent cardiovascular effects, particularly during pregnancy when levels of cholin-esterase (the enzyme which breaks down cocaine) are reduced (Shnider 1965) and cardiac tissue is primed with progesterone (increasing sensitivity to catecholamines) (Sharma et al. 1992). According to Wilkerson's work in the dog, low doses of cocaine increase blood pressure and heart rate while high doses take on the typical local anesthetic effects of slowing the heart and decreasing blood pressure (Wilkerson 1988).

Several groups have examined the cardiovascular effects of cocaine in the pregnant sheep model, which is considered the best model to study cardio-vascular changes in pregnancy since both the mother and the fetus can be monitored (Burchfield et al. 1991*b*; Moore et al. 1986; Woods et al. 1987). Cocaine administration to the mother results in dose-dependent increases in maternal blood pressure and heart rate and decreases in uteroplacental blood flow and fetal oxygenation (Woods et

al. 1987). Once plasma cocaine levels return to nonpharmacologic levels, the cardiovascular parameters return to normal.

Although there have been no studies published of human pregnancies under the conditions of cocaine abuse, scientists generally accept the sheep as a good model for drug effects in humans. The situation is somewhat different in the rat. That is, cocaine administered to the awake and freely moving mother increases blood pressure only transiently and actually decreases heart rate (Dow-Edwards et al. 1993; Morishima et al. 1992). Nevertheless, both the Morishima study and the Dow-Edwards study found that cocaine reduced blood flow to the placenta. The author's study (Dow-Edwards et al. 1993) also found that cocaine reduced oxygenation in the near-term fetus. Since hypoxia has, in and of itself, been demonstrated to produce long-term neurobehavioral alterations in the rat (Longo and Hermans 1992), the actions of cocaine on the cardio-vascular system and the reduction in uteroplacental blood flow could be responsible for a portion of the neurobehavioral effects currently attributed to cocaine's actions on neurotransmitters (see below). Some interesting data published by Koegler and colleagues (1991) demonstrate that blocking the vasoactive effects of cocaine blocks the decrease in ornithine decarboxylase, a key regulatory enzyme in the control of neural cell differentiation. However, until the timecourse and degree of hypoxia produced by cocaine are documented and appropriately modeled in the pregnant rodent, the contribution of hypoxia to the overall effect of cocaine on structural as well as neurobehavioral development in the rodent cannot be estimated. Therefore, although cardiovascular responses to cocaine are dampened in the rodent compared with humans, it is clear that cocaine's effects on the cardiovascular system interact with its effects on neurotransmitters and development.

In terms of neurobehavioral effects, scientists have relied on research in the adult animal to formulate hypotheses about the pharmacology and physiology of cocaine in development. Researchers utilizing animal models, most often the rat, have exerted an intense effort to determine the effects of cocaine on brain function and neurochemistry. This effort has greatly facilitated the understanding of cocaine's actions in the adult brain and provided direction for research into cocaine's developmental effects.

In the adult, cocaine has multiple and interactive effects. In addition to its local anesthetic effects, cocaine acts by inhibiting reuptake and

therefore metabolism of the three major neurotransmitters—dopamine (DA), sero-tonin (5-HT), and norepinephrine (NE)—thus increasing their concen-tration in the synapse and potentiating the effects of all three neurotrans-mitters. Effects of cocaine on the 5-HT system are even more complex due to uptake inhibition of the 5-HT precursor tryptophan and inhibition of the enzyme that synthesizes 5-HT, tryptophan hydroxylase. These effects would be expected to decrease serotonergic function over the long run.

At this time, the behavioral and neurochemical responses to cocaine are believed to be similar in rodents, nonhuman primates, and humans. For example, sensitization occurs in all three species; repeated exposure to cocaine at doses that initially produce simple behavioral activation eventually produce increasingly bizarre behavior that is quantitatively and qualitatively different from that initially observed (Post and Rose 1976). Sensitization is associated with specific neurochemical changes (i.e., a decrease in striatal DA concentration and alterations in the concentrations of DA receptors). The receptors can be increased or decreased depending on the brain region, duration of drug exposure, and the time since the last drug dose (Farfel et al. 1992; Goeders and Kuhar 1987; Kalivas et al. 1988; Kleven et al. 1988, 1990; Yeh and De Souza 1991). Generally, however, the concentration of DA and the numbers of DA type 1 (D_1) receptors are decreased.

While these neurochemical changes have been most thoroughly investigated in the rodent brain, parallel changes in DA receptors have been found in chronic cocaine abusers using positron emission tomography (PET) (Volkow et al. 1992) and in human postmortem samples (Hurd and Herkenham 1993). Therefore, there is empirical evidence that changes in the DA system following chronic cocaine exposure are parallel in human and rodent brain.

While DA is known to be important in the reinforcing effects of cocaine, all three neurotransmitters have been implicated as being important in the development of the CNS. In addition, the developing brain is quite different from the adult brain and some phenomena, such as sensitization, do not occur in developing organisms at all (Meyer and Yacht 1993). Therefore, while data collected in adult animals can serve as a guide for developmental studies, they clearly cannot replace developmental studies. The details of the neurobehavioral effects of cocaine exposure during development are found elsewhere in this monograph and the mechanisms of action have also recently been

reviewed (Dow-Edwards 1995). Due to the multiplicity of cocaine's effects, it is truly unique as a behavioral teratogen.

EXAMPLES OF CROSS-SPECIES COMPARABILITY

Historically, structural teratogens have been more thoroughly studied than functional teratogens. A wide range of potentially teratogenic substances has been examined for cross-species comparability and several excellent reviews have been published (Brown and Fabro 1983; Hemminki and Vineis 1985; Schardein et al. 1985). The authors generally conclude that although the specific structural damage produced by a given sub-stance may be different in animals compared with man, compounds that are found to be teratogenic in man are also teratogenic in animals and vice versa. For example, Brown and Fabro (1983) state that of the agents known to be teratogenic in humans, 97 percent of the tests in another single species also showed the agents to be teratogenic in that species. However, of 165 compounds believed to be nonteratogenic in humans, only 28 percent of the compounds were nonteratogenic in animals. Therefore, animal studies found relatively greater teratogenesis than human studies. This result is expected due to the greater numbers of animals that can be examined for events such as terata which have a low natural rate of occurrence. In addition, the compounds showing no terato-genesis in human may actually be teratogenic to a degree that is too low to be detected in the populations sampled. On the other hand, some sub-stances may be teratogenic only in animals due to species-specific metab-olism, pharmacokinetics, or developmental characteristics (see below).

A review of cross-species comparability for neurobehavioral endpoints was the subject of a meeting held in Williamsburg in 1989. This work-shop, "Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity," was cosponsored by the National Institute on Drug Abuse (NIDA) and the U.S. Environmental Protection Agency (EPA). The participants concluded that given the limitations of incomplete information available, particularly with regard to human dosing and exposure periods, the degree of across-species comparability for a wide range of compounds was considered remarkable. Several categories of behavior were evaluated, including motor development and function, cognitive function, sensory function, motivational/arousal behavior, and social function (Stanton and Spear 1990) (table 1). Across a wide range of developmental toxicants, similar effects were found for

each agent. In addition, certain measures tap processes that are closely comparable across several species; examples of these are given in table 1.

That is, for each neurobehavioral endpoint listed (e.g., acoustic and tactile startle), motor activity, sleep-wake cycles, habituation, short-term and long-term memory), good cross-species comparability was found for a range of compounds. A given toxicant may or may not have altered a given endpoint, but the same pattern of alterations was found in humans, nonhuman primates, and rodents for the endpoints listed (see Stanton and

TABLE 1. Comparability of endpoints in developmental neurotoxicology.

	Species		
Functional Category	Rodents	Nonhuman Primates	Humans
Sensory	--	--	Sensory psychophysics
	PI-ASR	PI-ASR	PI-ASR
	Sensory-evoked potentials	Sensory-evoked potentials	Sensory-evoked potentials
Motivation/ arousal	Activity	Activity	Activity
	Sleep-wake	Sleep-wake	Sleep-wake
	--	--	Impulsivity
	Seizures	Seizures	Seizures
Cognitive	--	--	Bayley MDI
	--	--	IQ
	--	Visual recognition memory	Visual recognition memory
	--	--	Language development
	--	Habituation	Habituation
	Habituation	Short-term memory	Short-term memory
	Short-term memory	Long-term memory	Long-term memory
	Long-term memory	Pavlovian conditioning	Pavlovian conditioning
	Pavlovian conditioning	SCOB	SCOB
	SCOB		
Motor	--	--	Bayley PDI
	Reflex development	Reflex development	Reflex development
	Locomotor development	Locomotor development	Locomotor development
	Motor control	Motor control	Motor control
	EMG	EMG	EMG
Social	Suckling	Suckling	Suckling
	Mother-infant contact	Mother-infant contact	Mother-infant contact
	Communication	Communication	Language
	Aggression	Aggression	Aggression
	Play	Play	Play
	Reproductive behavior	Reproductive behavior	Reproductive behavior

KEY: DEV = development; EMG = electromyograph; MDI = Mental Development Index; PDI = Physical Developmental Index; PI-ASR = prepulse inhibition of acoustic startle response; SCOB = schedule-controlled operant behavior.

SOURCE: Reprinted from *Neurotoxicol Teratol* 12:261-268, Stanton, M.E., and Spear, L.P., 1990, with kind permission from Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.

Spear 1990 for a comprehensive review). In theory, examination of these specific endpoints would produce closely comparable results for a given developmental toxicant. This also is the case for cocaine.

THE IMPORTANT ISSUES

Once the concept that certain behavioral measures tap similar processes across species is accepted, the next step is to determine the best model for cocaine administration during pregnancy. Three important issues allow one to model human development in animals and draw comparisons: pharmacokinetics, dose, and timing. Each outcome measure (dependent variable) may be sensitive to a unique set of circumstances. As seen in the adult, cocaine is a very complex drug with at least four major actions: inhibition of reuptake of DA and NE, effects on the 5-HT system, and local anesthetic actions. Data collected from studies in which cocaine is administered to adult rats indicate that the dosing schedule (continuous versus intermittent), the dose, the animal's gender, the conditions under which the dependent measures are collected, and particularly the time since the last administration are important in determining the magnitude and direction of the cocaine response. Even the route of administration is important in determining which systems respond to cocaine as well as the direction of the response.

PHARMACOKINETICS

Studying cocaine's effects in adult and developing animals is quite challenging due to the complex interactions of pharmacokinetics and pharmacologic responses. Within the last 2 years, rodent studies have appeared which indicate that cocaine effects in the adult depend to a great extent on the route of administration, presumably due to the importance of the rate at which cocaine occupies its receptors in the brain and the periphery. Whereas intravenous (IV) cocaine produces increased meta-bolic rates in components of the motor, sensory, and limbic systems, IP cocaine stimulates only the motor and sensory areas (Porrino 1993). Broderick (1992) has shown that IV and subcutaneous (SC) administra-tion of cocaine produce the opposite effects on extracellular DA (ECDA) levels in accumbens. That is, IV cocaine increased ECDA as expected, while SC administration actually decreased ECDA. When a drug's route of administration can determine not only the magnitude of the neurochemical alteration but also the direction, pharmacokinetic considerations take on additional significance.

What then is the best route of administration for use in cocaine studies in animals to maximize data comparability to the human condition? This question would be answerable if researchers knew precisely what plasma and brain cocaine levels were associated with the various routes of admin-istration in humans. Of course, brain cocaine levels would be almost impossible to determine in humans were it not for PET, which can deter-mine the uptake of labeled cocaine in human volunteers. Fowler and colleagues (1989) determined that uptake of cocaine was highly correlated with subjective ratings. Human brain cocaine levels can also be inferred by evaluating the high produced following various routes of administra-tion. Jones (1990) has examined human volunteers for differences in plasma (venous) cocaine levels following smoking and IV cocaine administration, and found that the maximum subjective high does not correlate with the maximum venous blood levels. Although smoking cocaine is widely acknowledged as the most reinforcing way to administer cocaine, the venous blood levels following this route (100 milligrams (mg) in pipe) were not as great as those following IV administration (0.6 mg/kg) and neither were the subjective ratings (Jones 1990; see table 2).

Recent data presented by Evans and colleagues (1995) also compared smoked and IV cocaine. They found the two routes produced roughly equivalent arterial and venous cocaine levels as well as similar cardio-vascular responses. The timecourses of the cardiovascular and subjective effects were highly correlated with the arterial plasma curve following both routes of administration. However, smoked cocaine actually produced somewhat lower subjective ratings of liking and feeling stimulated compared with IV cocaine. Although cocaine is probably most frequently abused by smoking, the available data on plasma cocaine levels do not provide physiologic support for the popularity of this route. Even though the human physiological data do not clarify the basic mechanism involved in producing cocaine's subjective effects, smoking is the best route to model in animal studies of development since smoking is generally considered the most popular route of administration.

There has been some progress in modeling crack smoking in animals, but this method of administration remains problematic. Work in sheep by Burchfield and colleagues (1991*a*) found that while a model of inhalation could be demonstrated, the peak plasma cocaine levels were one

TABLE 2. *Pharmacokinetics of cocaine: Comparison of species and routes of administration.*

Species	Route	Dose (mg/kg)	Peak Value (ng/ml)	Peak time	T1/2 (min)	Mat-fet ratio	Source
Human	IV	0.23	221	<5 min			Javid et al. 78
	IV	0.44	250	5 min			Evans et a. 95
	IV	0.46	308	<5 min			Javid et al. 78
	IV	0.6	550	10 min			Jones 90
	IV	1.47	1,000	<5 min	38		Barnett et al. 81
	IV	2.95	6,000	<5 min	87		Barnett et al. 81
	smoked	0.4	225	10 min			Jones 90
	smoked	0.67	160	5 min			Evans et al. 95
	IN	0.23	53	60 min			Javid et al. 78
	IN	0.91	115	30 min			Javid et al. 78
	IN	1.37	206	30 min			Javid et al. 78
	IN	2	350	70 min			Jones 90
	IN	2	170	90 min			Wilkinson et al. 80
	IN	2	160	60 min			Van Dyke et al. 78
	PO	2	290	80 min			Jones 90
	PO	2	242	65 min			Wilkinson et al. 80
	PO	2	209	60 min			Van Dyke et al. 78
Macaque-preg	IM	1.0	288	15 min	1.2 hr	7	Binienda et al. 93
Sheep	IV	2	20,000	1 min	3.4		Burchfield et al. 91*a*
	smoked	1.3	350	1 min	1.6		Burchfield et al. 91*a*
	smoked	1.5	902	1 min			Burchfield et al. 91*a*
Sheep-preg	IV	2	7,900	30 sec	1		Woods et al. 87
	IV	2	11,432	<1 min	5	26	DeVane et al. 91
Rat	IV	6	1,000		1.46 hr		Boni et al. 91
	IV	7.5	1,757	7.5 min			Pan et al. 91
	IV	8	610	15 min	0.3 hr		Nayak et al. 76
	IV	10	2,000		1.32 hr		Boni et al. 91
	IV chronic	7.5	1,970				Pan et al. 91
	smoked	0.26	95	45 sec	1.9 hr		Boni et al. 91
	smoked	1.54	205	45 sec	1.54		Boni et al. 91
	IP	7.5	130	15 min	108		Lau et al. 91
	IP acute	7.5	2,242	10 min			Pan et al. 91
	IP	15	230	15 min	72		Lau et al. 91
	IP	30	610	60 min	54		Lau et al. 91

TABLE 2. *Pharmacokinetics of cocaine: Comparison of species and routes of administration (continued).*

Species	Route	Dose (mg/kg)	Peak Value (ng/ml)	Peak time	T1/2 (min)	Mat-fet ratio	Source
	IP chronic	7.5	4,242	30 min			Pan et al. 91
	PO	7.5	130	45 min	90		Lau et al. 91
	PO	15	150	45 min	54		Lau et al. 91
	PO	30	250	30	96		Lau et al. 91
	SC	15	240	180 min	120		Lau et al. 91
	SC	20	490	4 hr	1 hr		Nayak et al. 76
	SC	20	494	4 hr			Mule & Misra 77
	SC-chronic	20	500	1 hr	2 hr		Nayak et al. 76
	SC-chronic	20	502	1 hr			Mule & Misra 77
Rat-preg	IV .	.33/min	1,660	na	4.5		Morishima et al. 92
	IV	3	3,725	30 sec			Mactutus et al. 94*b*
	IP	30	2,000	<30 min	46	<1	DeVane et al. 89
	IG	60	5,400	15 min	23	1.8	Dow-Edwards 90
	IG	30	1,000	15 min	44	1.4	Dow-Edwards 90
	SC	40	3,000	2 hr	2.8		Spear et al. 89
Mouse	IP	10	380	15 min			Shah et al. 80
	IP	10	2,000	5 min	16		Benuck et al. 87
	IP	25	7,000	5 min	16		Benuck et al. 87
Mouse-preg	IP	10	300	15 min			Shah et al. 80

KEY: IV = intravenous; IP = intraperitoneal; IM = intramuscular; SC = subcutaneous; IG = intragastric; IN = intranasal; PO = oral; preg = pregnant.

hundredfold lower than following IV administration. This difference was presumably due to the fact that the sheep do not intentionally inhale the smoke and do not hold their breath to establish high blood cocaine levels like humans do. Boni and colleagues (1991) compared IV administration and inhalation of cocaine in the rat and found that heart rate and blood pressure changes were generally dose dependent and temporally correlated with peak arterial cocaine concentrations. However, inhalation of cocaine by rats produced significantly lower plasma cocaine levels than IV administration, presumably because the rat also does not hold its breath. Therefore, at least in the rat and sheep,

smoking does not mimic cocaine pharmacokinetics produced by smoking in humans.

The next best route would be IV administration. Until recently, IV administration during pregnancy has been used only in studies of the acute effects of cocaine in sheep. Quite recently, however, a few groups have presented promising data from IV administration in the pregnant rat (Kunko et al. 1993; Mactutus et al. 1994*b*; Peris et al. 1992). The venous port system that Mactutus and colleagues (1994*b*) devised seems quite reliable, imparts minimal stress to the animal, and appears to be suitable for multiple daily injections without tethering the animals. Therefore, although smoked cocaine (crack) remains the most frequently used route of administration in humans, IV administration in animals most closely mimics the rapid rise and fall of plasma cocaine levels seen following crack smoking in humans (see table 2 for additional studies).

If a rapid delivery of cocaine to the brain is the administration pattern most desirable to model in adult animals, is it also the best pattern to model in developmental studies? At this time, it is unknown whether the rate of change in maternal plasma cocaine levels, the peak blood cocaine levels, or perhaps area under the time-concentration curve (AUC) is the most impor-tant factor for the production of a given developmental endpoint. While maternal drug-taking patterns may produce several rapid peaks in the plasma cocaine levels, the exposure of the fetus may be quite different.

The fetus does not metabolize cocaine as readily as the mother and thus would be expected to be exposed to the drug for a longer period of time than the mother. Nau (1986) has discussed the salient issues in this area and cites examples where peak plasma drug levels produce a given response (because continuous low levels of drug do not) or AUC correlates with the production of a given developmental endpoint. While IV cocaine in animals may model the situation in the adult human crack user, it is still too early to say whether this rapid rise in arterial and brain cocaine levels produces the greatest developmental toxicity. The effects of cocaine in the fetus are more difficult to measure and may be entirely unrelated to the effects in the adult. However, if peak plasma level is the major factor in determining developmental toxicity, then IV cocaine should be the most effective. If AUC is more critical, then SC cocaine would provide the greatest AUC for the plasma concentration versus time curve; SC administration results in a slow release of cocaine and peak plasma levels in about 3 hours (see table 2).

Intragastric (IG) administration, which is used in the author's lab, results in relatively rapid peak plasma cocaine levels (within 15 min) and pharmaco-logically effective plasma levels for about 90 minutes without the need for surgical intervention, which undoubtedly is somewhat of a stressor. In addition, IV administration produces a very narrow plasma concentration curve (a rapid rise and fall) but may not produce developmental toxicity simply because the plasma drug levels might be above threshold for only a very short time.

It will be several years before researchers know which route of administration reliably produces a given developmental insult since few laboratories are examining more than one route of administration. In addition, with the increasing awareness of animal rights issues, it is difficult, if not impossible, to obtain approval for within-laboratory replication.

DOSE

A quick glance at table 2 would show even the most naive investigator that there are many inconsistencies in peak value, peak time, and half-life (T n) even when cocaine is administered in equivalent doses via the same route of administration in the same species. For example, in three studies, cocaine was administered at 2 milligrams per kilogram (mg/kg) via oral and intranasal routes to human volunteers. In two studies, oral adminis-tration produced higher blood levels of drug while in the third, the Jones study, intranasal administration produced the greater blood cocaine levels.

In the rat, administration of greater amounts of cocaine resulted in relatively lower peak plasma values compared to humans. For example, Jones (1990) administered 0.6 mg/kg to human volunteers and obtained peak plasma levels of 550 nanograms per milliliter (ng/mL). Nayak and colleagues (1976) administered 8 mg/kg to rodents and obtained plasma values of 610 ng/mL. Thus a thirteenfold increase in dose in the rat results in an equivalent plasma level although identical routes of adminis-tration are used. Rees and colleagues (1990*b*) make the point that although there may be a great dichotomy in administered dose of a compound when comparing animals to humans, the internal dose produced is often quite different from the administered dose (see table 3). This is, of course, due to differential metabolism of the drug in animals and man. Differences in enzymes that metabolize cocaine, differences in

blood flow to the organs that metabolize cocaine, and differences in cardiac output all contribute to the production of differences in metabolism of cocaine.

Another issue is that of sampling. Evans and colleagues (1995) found tenfold higher cocaine levels in arterial blood than venous blood following both smoking and IV administration. Most rodent studies utilize trunk blood, which is a mixture of the two. One study (Lau et al. 1991) compared trunk blood to blood collected by snipping the tip of the tail and found that while the two were highly correlated, trunk blood contained 2.5 times more cocaine than tail tip blood across a wide range of administered doses. In other cases, investigators undoubtedly missed the peak of plasma cocaine by sampling too late or infrequently. For example, Nayak and colleagues (1976) found that the peak plasma level following 8 mg/kg cocaine was 610 at 15 min. Pan and colleagues (1991), on the other hand, administered 10 mg/kg cocaine IV and got levels of 1752 at 7.5 min. Mactutus and colleagues (1994*a*) found peak plasma levels at 30 seconds postinjection using the IV port for administration.

TABLE 3. *Administered versus internal dose comparison for phenytoin.*

	Human	Rodent
Administered daily dose	6-12 mg/kg	50-200 mg/kg
Measured blood levels	8-25 µg/mL	13-23 µg/mL

SOURCE: Data from Adams et al. 1990.

Another issue is that of chronic dosing. While virtually all human volunteers in the studies listed were acknowledged cocaine users, few rodent studies examined chronic exposure. However, these animal studies have shown that under some circumstances, chronic exposure facilitates the absorption process and produces either higher blood levels or a more rapid peak in plasma cocaine concentration. Pan and colleagues (1991) reported that previous exposure to IP cocaine almost doubled the peak plasma cocaine levels. Nayak and colleagues (1976) found that chronic SC cocaine had no significant effect on peak plasma

level but did decrease the time of the peak blood level from 4 hours to 1 hour. Therefore, the question of what dose to select to establish a relevant plasma cocaine level in an animal model relies on first establishing the human situation and then designing a dosing protocol in the animal model that mimics the human situation. However, even if this could be accomplished, differences in the timing of developmental events between animals and people must be considered before a given model is accepted as the best model.

TIMING

In development, the time during which the drug exposure occurs is obviously an important factor in trying to resolve issues of vulnerability. Although the general processes unique to nervous tissue during development are relatively similar for all mammalian species, the absolute time at which each event occurs differs by days or weeks across species. There is an orderly progression of events such as cell division, migration, differen-tiation, and cell death that is roughly similar for humans and rodents but the rate of occurrence of each process is different for each species.

Using gross anatomical features, links can be made across the species at specific developmental time points. Bayer and colleagues (1993) have matched the gross anatomical features of human embryo brains with rat embryo brains and established a comparative time table across the entire period of development. They have found that the state of maturation of the rat brain at birth, for example, is equivalent to the human brain at about 19 weeks (Bayer et al. 1993). It is during the postnatal period in the rat that the brain develops, as does the human brain during the last half of gestation. Therefore, although the basic sequence of development is similar in rat and human, the absolute time following fertilization at which a given event occurs and the time of birth in relation to the matura-tional state of the brain are quite different. On the other hand, the basic organization of the nervous system, the roles of the various cell groups that comprise nuclei, and the functions of these cell groups in behavior and physiology are similar across species. For example, the extrapyra-midal motor system performs similar functions in humans and rodents. The neurochemical composition in each brain system is similar across species, and with the limited information available in the human, the pharmacologic and neurochemical effects of stimulants are also similar (see above). Due to the similarities in the overall developmental

process-es and the similarities in pharmacology and function of the brains, rodent models have yielded a wealth of information about regulation of specific developmental events and how interference with one event can alter the course of development of many subsequent events.

As Dobbing (1968) demonstrated in the 1960s, the timing of the brain growth spurt or maximal expansion of the brain with respect to the day of birth is quite different for rodents and human beings. In humans, the brain growth spurt occurs just prior to the time of birth (completely within the month preceding birth) and in the rodent it occurs between 5 and 15 days postnatal. The human fetus opens its eyes at 25 weeks gestation (2/3 of prenatal development), and the rodent at 15 days postnatal. Late postnatal events such as the attainment of 50 percent of the adult weight in the cerebellum or 50 percent myelination of the corpus callosum are easier to compare since these occur at a time when tissue is available in both species. For example, the cerebellum attains 50 percent adult weight in humans at about 12 months of age and in the rat at about 15 days of age (Howard 1973). Myelination of 50 percent of the corpus callosum occurs at about 18 months in humans but not until 45 days in rats (Wiggins 1982). Both human babies and rodents undergo a postnatal maturation of the peripheral nervous system, the cardiovascular system, and the neuroendocrine system, all of which facilitate their adaptation to the environment. Thermoregulation, for example, takes 18 months to fully develop in humans and 18 days in rodents (Kleitman et al. 1937; Verlag 1962). Rodier (1994) has recently reviewed the postnatal development of a variety of reflexes across several species and concludes that the development of a specific reflex depends to a large degree upon the necessity of that reflex for the survival of the particular animal. Some species may be relatively precocious in one reflex and relatively delayed in another. Therefore, the appearance of reflexes should not be used to compare species in terms of timing of development of the brain.

The appropriateness of the model then depends upon the question being asked. For example, if the question pertains to the effects of cocaine on a specific brain region or nucleus, the model should examine cocaine administration during the period of cell division of the precursor cells of that region, the period of differentiation within that region, and the period during which connections with that region mature. Each region undergoes these processes at specific yet unique times and drug administration should be timed to encompass each event. If, on the other

hand, one wants to determine general effects on brain development produced by chronic, low-level exposure or even binge crack smoking, different models are appropriate.

Efforts to design a model must include consideration of the pharmacokinetics within the context of the differences in timing. For example, one may have decided to administer cocaine to a pregnant rat at a dose and via a route that result in pharmacologically relevant cocaine levels in the fetal plasma for 3 hours. Using Bayer and colleagues' (1993) comparison, events occurring between E11 and E17 in the rat that may take one day take two days in the human. Therefore, if the dose were administered between 11 and 17 days gestation in the rat, this 3-hour exposure would be equivalent to a person taking cocaine such that the fetus would be exposed for 6 hours. If, however, this dose producing a 3-hour exposure in the rat were administered during gestation days 18 to 22, it would be equivalent to human exposure lasting 1.75 days, since the time ratio changes to 1 rat day equaling 14 days of human development. The events in brain development which occur in the rat during a 3-hour period at this stage of development occur over a span of 1.75 days in the human. During postnatal life of the rat, a 3-hour exposure in the rat approximates a 1.1-day exposure in the human. Therefore, one can see that the use of once or twice daily dosing regimen during pre- and postnatal life of the rat are equivalent to exposure periods of different lengths in human brain development depending on when in development the dosing occurs. Certainly, every effort must be made to produce an animal model that mimics human exposure patterns. However, it will be impossible to produce the perfect model that would encompass the typical cocaine use pattern because of the differences in timing of developmental events, the fact that human use patterns in pregnancy are not accurately known, and the fact that single or multiple daily dosing approach translates into different exposure patterns depending upon the stage of development during which the drug is given.

EFFECTS OF GESTATIONAL COCAINE EXPOSURE

A summary of the reported effects of gestational cocaine exposure appears in table 4. The asterisks indicate similar effects in animal and human studies while the italics denotes differences. Although it is not possible to discuss each effect in this chapter, one can see that in most cases, similar effects have been attributed to cocaine in both animal and human studies. A more detailed comparison of two aspects of develop-

ment, the teratogenic effects and the effects on growth, was presented at the beginning of this chapter. Briefly, human and animal studies agree that cocaine is not teratogenic while they disagree with regard to its effects on growth. Animal studies find no effect on growth except at high doses, and clinical studies often find a positive association. In animals, reproductive effects are also identified only at toxic doses of cocaine, while in humans reproductive effects are frequently reported.

TABLE 4. *Summary of reported effects of gestational exposure to cocaine in humans and laboratory animals.*

	Human	Animal
Reproductive effects	*placental abruptions *IUGR *prematurity* *spontaneous abortion	*placental abruptions-HD *IUGR-HD *normal gestation length* *fetal resorption/death-HD
Early infant outcome	*low birthweight *few/no congenital malformations *respir. abnormal/SIDS *abnormal cardiac function*	*low birthweight-HD *few/no congenital malformations *respir/ abnormal *normal cardiac a & ß receptors*
Neural effects	*dec. head circumference* seizures/abnormal EEG *cranial infarct/hemor. *alt. brain metabolism *altered plasma catechols.	*little effect on brain weight* not reported *cranial hemorrhage *alt. brain metabolism *inc. NE turnover *complex DA changes alt. 5-HT, opiate, cholinergic, and somatostainergic systems disrupted gliogenesis
Behavioral effects		
Sensory	*abnorm. audit. evok. pot.	*abnorm. audit. evok. pot.-HD
Motivational/ arousal	orientation/state reg. *inc. reactivity* *alt. stress response	*inconsis alt. reactivity* *alt. stress response
Cognitive	*IQ dec.	*dec. classical condit *dec. sensory precondit. alt. DRL 20 & water maze impair. reverse condit. discrim.
Motor	*persist. primitive reflex* inc. extensor tone deficit in volit. movement	*inconsis. alt. reflex* inconsis. alt. activity
Social	dec interact. behav. *less play insecure attach.	*dec. play inc. submissive play demasculinization inc. aggressive behav.
Other		dec. reinforc. efficacy of cocaine lower threshold brain stimulation alt. drug responsivity

SOURCE: Adapted from Spear 1994.

KEY: DRL 20 = differential reinforcement of low rates of responding, 20-second interval. * = similar effect in human and animal studies; HD = occurs at high or toxic doses only. *Italic* indicates effects that are not similar in human and animal studies.

Early infant outcome measures appear to be similar across species with the exception of cardiac function. While cocaine-exposed infants have smaller heads and animals do not appear to be affected, both species show a variety of neurobehavioral effects that are remarkably similar (see table 4). The most speculative area is that of intelligent quotient (IQ). The reader is referred to Stanton and Spear (1990) for a complete dis-cussion of the comparison of assessments of human IQ and measure-ments used in animal behavior. Experts generally agree that in rodents, certain behavioral tests, including classical conditioning and maze performance, tap some of the same processes as those used in human IQ measures. Findings that cocaine alters these processes in rodents and IQ is reduced in offspring of cocaine and polydrug abusers (Griffith et al. 1994) indicate that the development of these complex processes in both species may be sensitive to the effects of cocaine.

Another interesting area is that of altered stress responsivity. Although the Spear chapter documents that prenatal ethanol exposure alters pituitary-adrenal responsiveness to stress, it also reveals that more work needs to be done in this area. Two groups have examined stress responsivity in the rodent following cocaine exposure. Both studies show that prenatal cocaine exposure decreases immobility in a forced swim test, a change consistent with an enhanced catecholamine or 5-HT function (Bilitzke and Church 1992; Molina et al. 1994). The author has noticed that intermediate doses of cocaine (30 mg/kg) appear to increase adrenal size while high doses (60 mg/kg/day) reduced adrenal size (Dow-Edwards, unpublished data). Owiny and colleagues (1991) demonstrated that maternal cocaine administration in sheep produced an increase in fetal adrenocorticotropin and an increase in maternal and fetal cortisol levels. Clinically, a pilot study by Mirochnick and colleagues (1991) showed that cocaine-exposed babies have increased levels of the NE precursor dihydroxyphenylalanine which the authors state may be related to an increased level of stress in the infants. Davidson Ward and colleagues (1991) have identified increased NE levels in cocaine-exposed infants, while Magnano and colleagues (1992) found no difference in basal cortisol levels in saliva of cocaine-exposed infants and a decreased response to a stressor such as a neuroexam or heel stick. Since there are conflicting reports of alterations in stress responses in the clinical literature (Eisen et al. 1991) and the handling of stress is a necessary skill for successful adaptation to life, there is clearly the need for additional work in this area, particularly in the basic sciences.

As with any study of drug-exposed newborns, health care providers have been concerned about neonatal abstinence since the pioneering work of Finnegan (1984) and the development of the Neonatal Abstinence Scale. To date, the majority of studies agree that prenatal cocaine exposure without opiate exposure does not produce significant neonatal abstinence. Only one animal study has addressed this point and it also found that prenatal cocaine did not alter ultradian rhythms at a time when prenatal methadone exposure did (Zmitrovich et al. 1992).

One final point can be used to compare animal and human data on prenatal cocaine exposure. Early clinical reports described abnormal ventilatory patterns and a significant increase in the occurrence of sudden infant death syndrome (SIDS) in populations prenatally exposed to cocaine (Chasnoff et al. 1989; Davidson Ward et al. 1986). However, reviews of large samples have shown that an increased incidence of SIDS is not associated with cocaine use during pregnancy (Bauchner et al. 1988; Kandel and Gaines 1991). Olsen and Weil (1992), however, have shown that prenatal cocaine exposure in guinea pigs does alter breathing patterns in a manner consistent with an increased tendency for SIDS. While cocaine may have some direct effect on the development of brainstem respiratory centers, the concomitant use of alcohol and cigarettes in cocaine-using pregnant women may account for many of the adverse effects of the drug. An interesting and new area of research is the use of PET in populations exposed to cocaine prenatally. Tyler and colleagues (1993) have found reductions in glucose utilization in about half of the children prenatally exposed to cocaine and other drugs. The author and colleagues' studies in rats show a very similar pattern of altered metabolism following prenatal cocaine exposure (Dow-Edwards et al. 1990). Use of techniques such as in vivo imaging that are identical in animals and humans (Blin et al. 1991) will certainly facilitate understanding of the developmental toxicity of cocaine, particularly once the confounding variables associated with clinical research on drug abusers can be controlled.

CONCLUSIONS

Certainly both clinical and preclinical research on prenatal cocaine exposure have a wide range of findings in common. Animal studies have been able to reproduce most clinical reports, particularly when toxic doses of cocaine are used; certainly there are individuals who use cocaine in the toxic dose range.

Several additional points can be made. First, as Vorhees (this volume) points out, the focus has been on the early postnatal period in both human and animal studies. Greater attention should be paid to long-term changes. Both animal and clinical investigators should improve control procedures (e.g., blinding of observers) and the reporting of important variables.

Within the animal literature, all in all, there is a low level of demonstrated reproducibility, perhaps due to the fact that no two authors examine the same set of endpoints. Although several authors have found significant effects that often parallel clinical findings, no two studies have found the same effects. The most robust effects of cocaine are seen when the organism is challenged, either pharmacologically or by using a more difficult task. Animal researchers have focused on one strain of rat and single daily doses. Consideration must be given to studies utilizing different routes of administration and dosing paradigms. Manipulation of environmental variables and polydrug models must also be developed to improve the relevance of the animal studies.

Lester and coauthors (this monograph) have elegantly described the clinical literature and illustrated that the mother and infant mutually regulate behavior in the context of the greater environment. The role of cocaine in this relationship is very complex. There is a biological effect in the mother during pregnancy and in the infant following exposure. This effect depends upon the dose and frequency of cocaine and other drugs during pregnancy as well as the drug-associated microculture. This microculture includes not only polysubstance abuse, poor prenatal care, and poor nutrition, but also sexually transmitted disease (STD).

Animal studies can address the biological and neurobiological effects of cocaine in the mother and infant, but the role of the drug abuse micro-culture on neurobehavioral outcome measures is much more difficult to quantify and model experimentally. Cocaine seems to make the child more vulnerable to the effects of a poor caretaking environment. Therefore, although the major focus of this chapter is on the effects of cocaine on the development of human and animal brain function, the reader must remem-ber that the biological and neurobiological effects of cocaine are only a part of the overall picture and the magnitude of effects may be different for each child examined.

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