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Developing brain and in utero cocaine exposure: Effects on neural ontogeny

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Abstract

Within the last decade, many investigators have focused on the physical, neurodevelopmental, and neuropsychological effects of prenatal cocaine exposure on infants and young children. Although inconclusive on many crucial issues, published studies reveal the beginnings of a profile of possible cocaine-related effects on neuropsychological functions subserving arousal and attention regulation. That profile is informed by preclinical studies in which important factors such as duration and type of exposure as well as environmental conditions may be more adequately controlled. In the developing brain, there are a number of candidate mechanisms that account for how prenatal cocaine exposure may interfere with neural ontogeny. This review focuses on the monoamine system, one of the primary sites of action of cocaine in the adult. In the developing organism, monoamines play critical trophic roles through all phases of central nervous system (CNS) ontogeny—cell proliferation, neural migration, growth, maturation, and synaptogenesis. Because of their trophic role in CNS ontogeny, cocaine effects on developing nervous system may be mediated in part through effects on monoamine system ontogeny. In turn, these effects may be expressed behaviorally in disrupted patterns of arousal and attention regulation given that these domains are connected intimately to monoaminergic systems.

In utero exposure to cocaine and its derivatives pose major perinatal health problems for a large number of infants and their mothers in the United States. Within the last decade, many investigators have focused on the potential physical, neurodevelopmental, and neuropsychological effects of prenatal cocaine exposure on infants and young children. These studies have utilized a variety of designs, including longitudinal, cross-sectional, case-control, and retrospective cohorts, have defined in multiple ways the independent variable(s) (i.e., the amount and duration of cocaine as well as other drug exposure), and have emphasized a host of different outcomes. (For a review of central methodological issues in studies of prenatal cocaine exposure, see Brooks–Gunn, McCarton, & Hawley, 1994; Frank, Augustyn, & Zuckerman, 1998; Lester, Freier, & LaGasse, 1995; Mayes & Fahy, in press; Neuspiel, 1995.) The oldest age of children in reported longitudinally maintained cohorts is between 8 and 10 years of age, but the majority of children in these longitudinally followed cohorts are only now reaching early school age (see, e.g., Richardson, 1998; Richardson, Conroy, & Day, 1996). Although still scant, inconsistent, or inconclusive on many crucial issues and marked by a number of methodological problems, published studies to date nonetheless reveal the beginnings of a profile of possible cocaine-related effects on neuropsychological functions subserving arousal and attention regulation and reactivity to stressful conditions (for recent reviews, see Frank, Bresnahan, & Zuckerman, 1993; Mayes, & Bornstein, 1995; Mayes, Grillon, Granger, & Schottenfeld, 1998; Richardson, Day, & McGauhey, 1993; Singer, Farkas, & Kliegman, 1992). That profile is further elaborated by findings from several animal mod-

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els in which crucial factors such as duration and type of exposure as well as environmental conditions may be more adequately controlled (Dow–Edwards, 1993; Dow–Edwards, 1991; Spear, 1995; Spear, 1996; Spear, Campbell, Snyder, Silveri, & Katovic, 1998). In particular, recent studies of prenatal and preweaning exposure in the rat point to direct effects of cocaine on the dopaminergic mediated circuitry that is particularly central to arousal regulation and attentional reactivity (Dow–Edwards, Yin, & Hurd, 1997; Friedman & Wang, 1998; Friedman, Yadin, & Wang, 1996; Howard, Fisher, & Landry, 1997; Minabe, Ashby, Heyser, Spear, & Wang, 1992; Wang, Runyan, Yadin, & Friedman, 1995; Weese–Mayer, Silvestri, Lin, Buhrfiend, Lo, & Carvey, 1993).

In this paper we review the state of knowledge regarding the neurobiological effects of prenatal cocaine exposure on the developing nervous system as elaborated through use of animal models. Studies in this area represent an important interface between basic studies of normal neural ontogeny and those of neuroteratology. Because cocaine is a potent central nervous system stimulant, understanding its effects on the developing brain not only explicates the possible neurodevelopmental impairments resulting from intrauterine exposure to a potential neurotoxin but also sheds light on mechanisms of normal neural ontogeny. This review focuses on neurobiological mechanisms purported to account for the neurotoxicity of cocaine in developing vertebrates. We examine the mechanisms for the effect of cocaine exposure on brain and cellular structure, neurotransmitter function, and genetic regulatory mechanisms. Wherever data are available, we point to possible neurobehavioral correlates for these alterations in structure and function.

Candidate Mechanisms for Cocaine-Related Neurobehavioral Teratologic Effects

There are several candidate mechanisms proposed for the effect of prenatal cocaine exposure on the ontogeny of neural systems and, by extension, for the cocaine-related neurobehavioral profiles. These are effects on monoaminergic system development; changes in neural growth factors; alteration of ion channel and monoamine transport development; effects on other neurotransmitter systems (such as the cholinergic system) and on neuropeptides (including substance P), dynorphin, gamma aminobutyric acid (GABA), and glutamate sites; or alteration of immediate early gene expression (Kosofsky, Genova, & Hyman, 1995a,b; Nestler, Gao, & Tamminga, 1997; Olsen, 1995).

Cocaine also has potent vasoconstrictive effects that may have a more generalized and less system-specific hypoxia-related deleterious effect on neural growth. The effect on central and peripheral noradrenergic systems accounts for the cardiovascular effects of cocaine, including tachycardia, hypertension, and increased risks for strokes and myocardial infarctions and arrhythmias. Thus, in utero cocaine exposure may compromise fetal brain development through an effect on placental vascular function with decreased placental blood flow and consequent fetal hypoxemia and possibly ischemic injury. Similarly, cocaine-related noradrenergic effects on developing fetal vasculature may also compromise blood flow to the developing brain (Koegler, Seidler, Spencer, & Slotkin, 1991; Woods, Plessinger, & Clark, 1987). This more general level of effect through fetal hypoxemia or relative ischemia may not be as specifically directed to one region of the brain over another, and the severity of effect, if any, will depend particularly on the timing of the exposure and the level of relative hypoxemia.

Another group of mechanisms of in utero cocaine effect on neurodevelopmental outcome is also more general but unique to the human model. Substance-abusing adults rarely use cocaine in isolation. Most often, cocaine abuse is combined with other potential neuroteratogens including alcohol, marijuana, and tobacco. While there are no studies modeling various combinations of polydrug exposure in animals, it is reasonable to hypothesize that interactions among different drugs may produce both potentially neurotoxic metabolites as well as directly additive effects on neural development. Related to human sub-

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stance abuse are other more general health and environmental factors that have effects on fetal health and development. These include poor maternal nutrition (in part reflecting the appetite suppression effect of cocaine) and, more often than not, maternal poverty and environmental chaos that may contribute to postnatal neglect and poor parenting, factors that are themselves developmentally compromising. These levels of effect unique to humans cannot be adequately modeled in animals but do confound efforts to attribute any neurobehavioral impairments found in prenatally cocaine-exposed infants and young children to cocaine alone. The methodologic dilemmas in human studies of prenatal cocaine exposure are reviewed in detail elsewhere (Brooks–Gunn et al., 1994; Frank et al., 1998; Lester et al., 1995; Neuspiel, 1995).

In this review, we focus primarily on the effects of prenatal cocaine exposure on monoaminergic system function and ontogeny (including the catechoamines dopamine and norepinephrine and the indoleamine serotonin), though several of the aforementioned candidate mechanisms may also be influential in the neurobehavioral profiles of altered arousal and attention regulation. Importantly, the nonspecific but frequent mixture of acute and chronic stress characterizing the postnatal caregiving environments for many prenatally exposed children may also have enduring effects on attention and arousal system ontogeny, perhaps through some of the same monoamine-related mechanisms.

Neuropharmacology of Crack and Cocaine in Adult Brain: Action at the Level of the Synapse

The functional anatomy of the synapse

At the most basic level of analysis, cocaine and its derivative form crack are central nervous system (CNS) stimulants with effects very similar to those of amphetamines. (Unlike amphetamines, however, cocaine also has local anesthetic effects which will not be reviewed further, but for more details see Post & Weiss, 1988; Reith, 1988.) Centrally, cocaine acts primarily at the level of the synapse. The primary effects are at the level of the presynapse, but by interfering with presynaptic function cocaine also affects postsynaptic activity. In the mammalian nervous system, the most common form of neuronal communication is the chemical synapse, whereby electrical discharge in the presynaptic neuron releases a chemical neurotransmitter into the synaptic cleft or space (Shepherd, 1994). This neurotransmitter diffuses across the cleft and interacts with a specific receptor protein on the surface of the postsynaptic neuron. Receptors for specific neurotransmitters are found on both the pre- and postsynaptic membranes, the former as autoreceptors modulating the ongoing release of neurotransmitter through feedback loops and the latter translating the chemical message into electrical signals. The synapse is thus bidirectional.

The response of the postsynaptic neuron is terminated not at the level of the neurotransmitter–receptor bond on the postsynapse but rather by reuptake of the neurotransmitter by the presynapse or by inactivation by enzymes on the surface of the postsynapse. With either mechanism, removal of the neurotransmitter is necessary for the communication between nerve cells to be terminated. Blocking reuptake is the most important mechanism of cocaine-related effect at the level of the synapse. With reuptake, transporters specific to a given neurotransmitter take that remaining in the synaptic cleft back into the intracelluar space of the presynapse.

Neurotransmitters are grouped into seven categories: (a) acetylcholine, (b) catecholamines (dopamine, norepineprhine), (c) indole amines (serotonin), (d) histamine, (e) inhibitory amino acids (GABA), (f) excitatory amino acids (glutamate and aspartate), and (g) neuropeptides (opioids including dynorphin and enkephalin, nonopioids including substance-P, thyrotropic releasing hormone). Cocaine acts primarily on the second and third groups, the monoamine neurotransmitters. However, cocaine also interacts with the neuropeptides, GABA, and glutamate receptors (Kreek, 1996; Shippenberg & Rea, 1997; White, Hu, Zhang, & Wolf, 1995; Ye, Liu, Wu, & McArdle, 1997), though very little work has been done on these systems in the

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fetal animal model. Parenthetically, cocaine also acts at the level of ion-channel transmission in the adult (Reith, 1988), though again little to no work is available for the effects on developing neural systems. Neurotransmitter systems may be broken down into several functional units for the purposes of study. These include (a) synthesis and concentration of neurotransmitter, (b) affinity and mRNA for the transporter (reuptake process), (c) mRNA for the postsynaptic receptor, (d) postsynaptic receptor density, (e) postsynaptic receptor binding or affinity for the neurotransmitter, and (f) level of activation in neurotransmitter specific brain regions as measured by *glucose uptake* or by the induction of genes (immediate early genes [IEG]). Neurotransmitter systems can be also studied by using a variety of agents that attenuate or enhance transmitter release or compete with other agents for binding to the receptor (or transporter). Most recently, the availability of so-called knockout models, in which animals are deficient in the gene for a specific synaptic component such as a receptor, provide another approach to studying neurotransmitter function (e.g., Xu, Hu, Cooper, White, & Tonegawa, 1996).

Cocaine and synaptic function

In the mature brain, cocaine and crack act at the level of the synapse to block reuptake of monoaminergic neurotransmitters (dopamine, norepinephrine, and serotonin) at the presynaptic junction. Presynaptically, cocaine is more efficacious in blocking the reuptake of serotonin (5-HT) as compared to the catechoamines dopamine (DA) and norepinephrine (NE; Lakoski & Cunningham, 1988). The mechanism by which cocaine blocks monoamine reuptake involves blocking the action of the presynaptic transporter protein that takes neurotransmitter back into the presynaptic neuron. In the short term, blocking reuptake effectively leaves a greater concentration of monoamines in the synaptic cleft and thus the potential for increased synaptic activity and increased neurotransmitter turnover. In addition, stimulants such as cocaine also accelerate presynaptic release of catecholamines (DA and NE; Kosten, 1990).

Anatomy of the monoaminergic system

The monoamine system has been mapped in detail in both animal and human studies (e.g., Nieuwenhuys, 1988). The dopaminergic, serotonergic, and noradrenergic systems are related to one another and have a different balance of inhibitory and excitatory effects, depending on the region of the brain being studied and the combinations of other receptors on groups of neurons in that region. The norepinephrine and serotonin systems spread throughout the brain, while dopamine circuits are more specifically targeted. The more ubiquitous distribution of norepinephrine and serotonin pathways suggests that the effects of cocaine on these pathways should have more general consequences, while effects on the dopaminergic system may be more specific. Primary circuits for all three neurotransmitters originate in the brain stem—dopamine from the substantia nigra and ventral tegmental area, norepinephrine systems in the locus coeruleus and other nuclei in close proximity, serotonin from the raphe nuclei. The following areas of the brain will be critical in the remainder of this review for localizing the regions of the brain where cocaine is pharmacologically active and where the monoaminergic system is central. (For a more thorough neuroanatomic and functional overview, see Alexander, DeLong, & Strick, 1986; Burt, 1993; Nieuwenhuys, Voogd, & van Huijzen, 1988; Parent & Hazrati, 1995.)

Above the monoaminergic nuclei in the brain stem (mesencephalic or midbrain region) is the diencephalon. This region below the cortex contains the thalamus, hypothalamus, and so-called limbic system. The thalamus, made up of multiple discrete but interconnected nuclei, receives almost all the signals from the midbrain (and other lower regions in the brain stem) before transmission to the cortex. The thalamus also receives a continual traffic of signals from the cortex (corticothalamic pathways). Nearly all sensory signals are relayed through the two-way connections between thalamic structures and

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cortex. The limbic system (limbic meaning "border") contains a number of structures involved in the regulation of states of arousal and emotion. The amygdala, hippocampus, cingulate cortex, and nucleus accumbens are among the structures of the limbic system most studied in relation to cocaine effects in both the adult and developing animal. Deep inside the cortex above and lateral to the thalamus are the basal ganglia linked to the limbic system in part through the nucleus accumbens. The basal ganglia are involved in the regulation and coordination of movement (see below). The most important structures within the basal ganglia are the caudate nucleus and the putamen (together referred to as the striatum or dorsal striatum) and the globus pallidus. The amygdala lies at the tip of the caudate nucleus. The term striatum is also sometimes used to refer to the caudate, putamen, amygdala, and globus pallidus as a group, and in some systems the nucleus accumbens is referred to as the ventral striatum. The cortex above the basal ganglia receive extensive efferent innervation from all regions already mentioned and send afferent signals back to each of these regions either directly or by way of circuits crossing through several different structures. (For more detail on neural circuitry, see Alexander et al., 1986, and Parent et al., 1995.) The prefrontal cortex also receives extensive input from these monoaminergic rich regions.

Monoamine system and cocaine

The dopamine system is particularly central to the effects of cocaine on both adult and developing brain. Dopamine neurons have long been associated with the initiation of behavior, reward, and motivational processes (Koob, 1996). Two major dopaminergic circuits are involved in the action of stimulants. The nigrostriatal dopamine system originates in the substantia nigra and projects to the caudate nucleus and putamen (dorsal striatum). The degeneration of this system is implicated in Parkinson's disease and is also important for the focused repetitive behaviors associated with high doses of stimulants (Creese & Iverson, 1974; Koob, 1996). These pathways are also associated with the planning, initiation, and coordination of voluntary movement and complex behavioral repertoires (Graybeil, 1990). The mesolimbic dopamine system projects from the ventral tegmental area of the midbrain to the limbic forebrain (including the nucleus accumbens, olfactory tubercle, amygdala, and frontal cortex). This second dopaminergic system has been most implicated in activation and locomotor behavior (LeMoal & Simon, 1991) and stimulant-induced locomotion (Koob, 1996). The regions involved in the mesolimbic system, especially the amygdala and the prefrontal cortex projections from the amygdala, are also important in the regulation of stress response and emotional reactivity. The mesolimbic dopaminergic circuits are probably critical for the stimulant induced euphoria and for the reinforcing (addictive) properties of drugs (Goeders & Smith, 1983; White, 1996; Wise, 1984). The nucleus accumbens (ventral striatum) within the mesolimbic system seems particularly important for the reinforcing properties of stimulants because animals will self-administer large amounts of cocaine to this particular region even to the point of seizures and death (Corbett & Wise, 1980).

Dopamine acts at specific dopamine receptor sites, and there are at least five dopamine receptor types that cluster into D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) subfamilies (Civelli, Bunzow, & Grandy, 1993). D_1 and D_2 receptors are the most extensively studied. Dopaminergic neurons from the dorsal and ventral striatum have efferent neurons to the substantia nigra (the striatonigral system) and to the thalamus by way of the globus pallidus (the striatopallidal system). Each of these systems differs in dopamine receptor subtypes and in neuropeptide receptors. The striatonigral system has predominantly D_1 receptors and the neuropeptides dynorphin and substance P, while the striatopallidal system has D_2 receptors and the neuropeptide enkaphalin. These two dopamine systems may function differently in response to cocaine exposure in developing brain (see below).

The serotonin system originating from the raphe nuclei of the brain stem project widely to the cortex, and to memory and emotion

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regulation areas such as hippocampus, thalamus, and amygdala. Just as with dopamine, the effects of cocaine on serotonin systems appear to be through the inhibition of reuptake processes and increased release (Lakoski & Cunningham, 1988). There are at least four classes of serotonin receptors in the brain (5-HT_{1-4}) with subtypes of 5-HT_1. Most studies of the action of cocaine have investigated effects on 5-HT_{1a} and 5-HT_2, the former present in high density throughout the hippocampus, amygdala, hypothalamus, and cortex and the latter more concentrated in the cortex. Serotonin pathways are implicated in the regulation of arousal and sleep states and in the regulation of circadian rhythms, and serotonin agonists in the form of reuptake inhibitors are potent antidepressants (Frazer & Hensler, 1994).

The norepinephrine system is crucial to the regulation of behavioral state, sensory processing, aspects of memory, and attention regulation (Grace, Gerfen, & Aston–Jones, 1998). The noradrenergic system has projections throughout the limbic and corticothalamic system with wide distribution of α- and β-adrenergic receptors. Earlier work had suggested that the norepinephrine system was important for the reinforcing effects of cocaine and related drugs, but subsequent studies have suggested dopamine as the more critical catecholamine for that role (Kosten, 1990; Wise, 1984). The noradrenergic pathways may be most critical for the nonspecific activating effects of cocaine and the peripheral effects on overall vascular tone and cardiac function (Gawin & Ellinwood, 1988). Norepinephrine is a potent vasoconstrictor, and acute use is associated with elevated blood pressure, increased cerebral vascular pressure, and tachycardia.

Arousal Regulation: Relation to Monoaminergic Regulation

In both adults and children, monoaminergic-rich regions of the brain (e.g., locus coeruleus, raphe nuclei, substantia nigra, striatum, amygdala, prefrontal and posterior parietal cortex) are integral to arousal and attention regulation (Coull, 1998; Gonzalez–Lima, 1989; LeDoux, 1987; Robbins & Everitt, 1995; Robbins, Granon, Muir, Durantou, Harrison, & Everitt, 1998). The concept of arousal regulation as a state of CNS activation is central to theories of attention and sensory processing and stages of sleep and wakefulness and is one of longstanding interest and importance to studies of infants and young children (Rothbart & Posner, 1985). Originally proposed as a unidimensional continuum mediated by a diffuse neural network in the brain stem (reticular formation) projecting to and receiving both inhibitory and excitatory feedback from the thalamus and forebrain, arousal regulation was the mechanism whereby stimuli of different intensity and salience regulated cortical activation (Hebb, 1955). Currently it is clear that the arousal regulatory system is neither unimodal nor based in a single neural system. Rather, several different but interactive systems receive neurochemical inputs from discrete neural groups within the so-called reticular formation and project to different regions and layers of the cortex (Marrocco, Witte, & Davidson, 1994; Robbins & Everitt, 1995; Robbins et al., 1998).

For studies of both prenatal cocaine exposure and cocaine addiction, at least two components of the arousal systems are crucial. One involves primarily the norepinephrine system projecting from the locus coeruleus to the prefrontal and posterior cortex and hippocampus. Another involves the mesolimbic and mesostriatal dopamine systems that also have extensive cortical projections from the striatum and limbic region including the amygdala. The former norepinephrine system has a central role in supporting and protecting an ability to discriminate among stimuli during distracting, novel, or anxiety-provoking circumstances (Robbins et al., 1998), while the latter DA system is important to reward motivation and may be co-opted in the reinforcing (addictive) properties of drugs (Goeders & Smith, 1983; Koob, 1996; White, 1996). The amygdala complex within the dopamine system is associated with the mediation of response to fear, anxiety, and other negative affects (Aggleton, 1992). It may be that the dopamine system is the more basic or first-

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level system regulating arousal in response to needs or emotions such as fatigue, hunger, distraction, anxiety, and stress, while the norepinephrine system serves as a second line of defense, as it were, regulating and compensating for fluctuations in the first-level dopamine system (Robbins, 1984). Also, strictly labeling these systems by a single neurotransmitter belies the overall complexity and contributions of other neurochemicals within the same circuitry. For example, serotonin pathways may serve to dampen the actions of both norepinephrine and dopamine systems, serving as another line of defense against hyperarousal (Robbins, 1984).

As the level of cortical activation increases through these mutually interactive arousal systems, performance improves on a variety of dimensions including anticipation (shifting of attention), planning, working memory, and organization (executive functions; prefrontal cortex). These relations between arousal and cortical function are mediated in part through interdependent dopamine (D_1 receptor) and NE effects (α_2) on the prefrontal cortex (Arnsten, 1997). This facilitative effect may be balanced and modulated as well by an opposing, inhibitory D_2–α_1 interaction (Grace et al., 1998). But in situations of overwhelming stress or anxiety (hyperarousal), these mutually interactive systems may not be able fully to preserve these cortical functions and aspects of attention and other higher order reasoning and discriminative abilities deteriorate specifically in hyperaroused states (Arnsten, 1998). Excessive D_1 and α_1 activity diminishes prefrontal cortical function (Arnsten, 1997). This deleterious effect of excessive D_1 activity is buffered in part by the NE α_2 arousal system (Murphy, Arnsten, Jentsch, & Roth, 1996). However, with sufficient hyperarousal the D_1–α_2 system in the prefrontal cortex is taken "off-line" by increased α_1 and possible D_2 activity. Thus, the interactive dopamine–norepinephrine pathways produce a U-shaped response pattern typically associated conceptually with arousal; that is, diminished or excessive arousal impairs performance with an optimal range for performance in the middle of the arousal curve. At the same time, in a hyperaroused state other more automatic functions basic to fight–flight response are enhanced, including dopamine-related functions in the amygdala and hippocampus (where basic circuitry for fight–flight and memory consolidation are based) and norepinephrine-related functions for vigilance in the posterior cortex.

In the course of development, the threshold for hyperarousal increases as infants and children are gradually able to tolerate more intense and more varied stimulation and experiences, but this threshold always remains individually variable and subject to enduring change based on overwhelmingly traumatic or stressful experiences or illness or toxin exposures at different phases of development. Indeed, several models are now proposed for how acute and chronic stress may lead to enduring alterations in the threshold for activation of the amygdala complex (dopamine system; Davis & Lee, 1998; Goldstein, Rasmussen, Bunney, & Roth, 1996) and the norepinephrine arousal system and thus altered thresholds for hyperarousal (Valentino, Curtis, Page, Pavcovich, & Florin–Lechner, 1998). Based on the effects of cocaine on developing monoamine systems that will be detailed below, it is plausible to hypothesize that for prenatally cocaine-exposed infants and children, there may be enduring alterations in the balance between and within the norepinephrine and dopamine arousal systems. In turn, the balance between facilitative and inhibitory effects on prefrontal cortex and attentional functions may also be permanently altered and more apparent under stressful or arousing conditions, which often characterize the caregiving environments for many prenatally exposed children.

CNS Ontogeny

Basic principles

CNS development reflects a complex interaction among genetic factors, neurochemical substrates, and environmental conditions (Kosofsky, 1991). Eight stages describe the processes that occur in each part of the developing brain (Cowan, 1979): neural plate induction, neuronal and glial cell proliferation,

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cell migration, cell aggregation, neuronal maturation, neuronal connectivity (including synaptogenesis), cell death, and process elimination (pruning). Within each of these phases, there are parallel processes of metabolic differentiation and maturation and the onset–offset of each stage is probably regulated by genes taking their regulatory cues from the immediate neurochemical (and experiential) environment. As a more general map in humans, cell proliferation occurs between 2 and 4 months gestation for neurons and 5 months gestation to 1 year postnatally for glia; neuronal migration takes place primarily between 3 and 5 months gestation. Between 6 months gestation to several years postnatally, the brain is in a protracted organizational phase, establishing neuronal connectivity and pruning less utilized connections or synapses to enhance other patterns of connectivity (Volpe, 1987). The timing (gestational or postnatal) of potentially toxic exposures determines the possible developmental consequences. Exposures occurring during the first half of gestation affect cytogenesis and histogenesis, while those exposures occurring in the latter half of pregnancy and postnatally influence growth and structural–functional differentiation (Evard, de Saint–Georges, Kadhim, & Gadisseux, 1989). Exposures throughout both periods have "interactive" effects, inasmuch as altering early events during the cytogenesis phase will also alter events downstream that are regulated by the completion of earlier phases. Brain development in the second half of gestation and the early postnatal period is characterized by both *progressive* (e.g., synaptogenesis and neuronal maturation) and *regressive* (e.g., cell death and pruning) processes. Blocking, delaying, extending, or shortening either progressive or regressive events will have probable (and different) effects on immediate structure–function relations, on related genetic regulatory processes, and on neuromaturational events downstream that are dependent on earlier events.

Monoamines and CNS ontogeny

The monoamine systems that are most involved in the neuropharmacologic effects of cocaine on the adult brain are also crucial to neural ontogeny in all phases of development. In the immature brain, many neurotransmitters play a role entirely different from their role in the mature brain. They act as developmental regulators, and neurotransmitter receptors have been found in fetal brain very early in gestation. Those areas maturing first in terms of cell division and differentiation are also the regions that acquire receptors for monoamines and other neurotransmitters first. In most species at birth, brain stem receptors are more mature than cortical receptors, which are in turn more mature than those in the cerebellum (Whitaker–Azmitia, 1991). Different receptor types can also develop at different rates and serve very different functions in the developing brain than they do in the mature animal.

Monoamines play critical trophic roles through all phases of CNS ontogeny—cell proliferation, neural migration, growth, maturation, and synaptogenesis (Lauder, 1988; Lauder, 1983; Mattson, 1988). Monoamine cell groups in the brain stem appear very early in fetal development. For example, in the rat, by the 2nd week in gestation norepinephrine neurons are found in the locus coeruleus and serotonin neurons in the raphe nuclei. By this same time, dopamine neurons in the substantia nigra are beginning to synthesize dopamine (Lauder & Bloom, 1974). In humans, by the end of the 2nd month of gestation (8 weeks) serotonin and norepinephrine neurons are detectable (Pickel, Specht, Sumal, Joh, Reis, & Hervonen, 1980). Dopamine neurons appear in the substantia nigra and ventral tegmental area during the 5th week and in the striatum during the 7th to 18th weeks, and dopaminergic projections from the midbrain into the striatum are present from Week 6 (Verney, Zecevic, Nikolic, Alvarez, & Berger, 1991). In rhesus, mRNA for the dopamine transporter is present between 45 and 60 days gestation (late 1st to early 2nd trimester; Choi & Ronnekliev, 1996). When monoamine tranporters are present and presumably active, this is also the site for cocaine binding to inhibit reuptake.

Suggestive evidence for the role of monoamines and their receptors in fetal brain de-

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velopment is that some receptors may be overexpressed in the immature brain and expressed in regions where they are absent in the adult (Whitaker–Azmitia, 1991). For example, for some receptor subtypes the greatest number of receptors occurs at a time when functional synapses are not present. In both the rat and human, levels of serotonin receptors peak in fetal or early neonatal life and then decline to adult levels (Gross–Isseroff, Salama, Israeli, & Biegon, 1990; Whitaker–Azmitia, Lauder, Shemer, & Azmitia, 1987). Similarly, dopamine D_1 and D_2 receptors are more numerous in the immature brain in both human and rat (Miller & Friedhoff, 1986; Seeman et al., 1987). (Indeed, as a general principle, this observation of early overexpression is true of many components of the developing nervous system.) Because of their trophic role in CNS ontogeny, it seems reasonable to hypothesize that cocaine effects on developing nervous system may be mediated in part through effects on monoamine system ontogeny and monoamine function at the level of neurotransmitter and receptor synthesis, receptor sensitivity and binding, and monoamine system projections to other regions. These effects at a cellular, structural, and functional level may also be expressed behaviorally in disrupted patterns of arousal and attention regulation, given that these domains are connected intimately to monoaminergic systems.

In brief, during early neuroproliferative and migratory phases, monoamines play central roles. Early in gestation, neurons migrate from a proliferative zone to the cortex and associated structures. Migration is accomplished by following elongated lattices of nonneuronal tissue, the radial glial cells (Rakic, 1971; Rakic, 1988). Neurons reach their destination, as it were, by moving along in close adhesion to radial glial columns. The genesis of the radial glial unit so essential to the migratory phase is regulated by the monoaminergic system (Lidow & Rakic, 1994, 1995; Lidow & Wang, 1995). During later phases of neuronal maturation and synaptogenesis, monoamine receptors are fully functional, and the monoamine specific transporters that are involved in reuptake are also present and functional. Manipulation of monoamine receptors during this latter part of neural ontogeny (late 3rd trimester and early infancy in the human) with agonists or antagonists can result in long-term alterations in the function of these regions and their associated pathways (Friedhoff & Miller, 1983; Rosengarten & Friedhoff, 1979). These mechanisms which will be covered in greater detail below (under the discussion of specific monoamines) involve both the direct effect of the monoamines on cell growth and maturation and enhancing or diminishing neural connectivity and indirect effects through monoamine-regulated release of nerve growth factors such as serotonin-mediated S100β.

Parenthetically, some of these effects may be modeled by studying non-cocaine-related manipulations of the monoamine system. For example, inhibition of serotonin synthesis in raphe neurons results in delayed differentiation of cells spatially and temporally associated with developing serotonin axons (Lauder, Towle, Patrick, Henderson, & Krebs, 1985). Addition of serotonin to in vitro cultures of cortical and hippocampal cells results in glial proliferation and synaptogenesis (Chubakov, Gromova, Konovalov, Sarkisova, & Chumasov, 1986). Studies with specific neurotoxins that deplete brain catecholamines in the early postnatal period for the rat produce a variety of changes in developing brain regions innervated by dopamine and norepinephrine, including alterations in cortical thickness and cell density (Kalsbeek, Bujis, Hofman, Matthijssen, Pool, & Uylings, 1987) and increased dendrite development of serotonin neurons in the cortex and striatum (Towle, Criswell, Maynard, Lauder, Joh, Mueller, & Breese, 1987).

In Utero Cocaine Exposure and Developing Neural Systems

Given the effects of cocaine on monoaminergic system function and the trophic role of monoamines in brain development, it is reasonable to hypothesize that cocaine effects on developing nervous system may be mediated in part through effects on monoamine system ontogeny and monoamine function at the level

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of neurotransmitter and receptor synthesis, receptor sensitivity and binding, and monoamine system projections to other regions. There is good accumulated evidence in animal models now to support this supposition. The majority of animal models have used the rodent with the rabbit and primate as second and third choices in order of frequency of use. Exposure designs vary, including prenatal exposure, equivalent to roughly the first 2 trimesters of human development, and postnatal or preweaning exposure models in the rat and mouse, equivalent to the 3rd trimester in the human. Additionally, with postnatal maturation there is ongoing monoaminergic system development, and there may be further shifts in neurotransmitter synthesis and receptor function with some neonatal effects apparently disappearing or reversing in the direction of effect from attenuation to upregulation or vice versa. Thus, it is important to pay careful attention both to when the exposure occurred in the animal model and when the brain was examined (fetally or postnatally, immediately after cessation of the exposure or with some time between exposure and brain study, preweaning or postpubertal).

An important caveat pertains to the regions of the brain studied. While there are significant studies of the cortex, the majority of studies have focused on monoaminergic rich regions—those with originating monoamine nuclei and those with central monoaminergic projections. Thus, striatum, amygdala (and associated limbic structures), hippocampus, and hypothalamus, as well as the midbrain monoamine nuclei, are more extensively studied regions than areas of the cortex. A related caveat pertains to work on monoamine function itself. Initial studies focused on monoamine production and absolute levels in brain regions pre- and postnatally. Fewer earlier studies have also focused on receptor density and sensitivity. More work recently is beginning to examine receptor binding affinity, receptor sensitivity to known agonists and antagonists, maturation changes in receptor function given early prenatal alterations, and the expression of genes for receptors and transporters. Studies on genetic expression for other neurotransmitters such as the neuropeptides and the effects of cocaine on immediate early gene expression (Sheng & Greenberg, 1990) are just beginning.

As a final caveat, we will not review in detail the methodological issues that are important in animal models of in utero cocaine exposure. Besides the relative merits of one neurochemical method or approach over another, there are many critical experimental issues that surely influence the weight to give certain groups of findings. We cite only those which are most similar to those in humans. These include the dose and route of cocaine administration—and how that route affects the rate at which peak levels are obtained, the absolute peak level, and the duration of level above a certain threshold. Intraperitoneal administration results in a very different blood level compared to subcutaneous, and both are different from gastric lavage. Furthermore, regardless of route of administration, fetal cocaine levels are different from the maternal one (lower for subcutaneous administration [Spear, Kirstein, & Frambes, 1989] but higher for intraperitoneal [DeVane, Simpkins, Miller, & Braun, 1989]). Cocaine is also an appetite suppressant in animals and thus, for both the pregnant mother and the postnatal pup in the first 2 weeks after birth, controlling for amount of food intake using pair-fed and non-pair-fed comparison groups may be important (Galler & Tonkiss, 1998). However, the methodologic standards defining nutritionally controlled comparison groups are far from agreed upon (e.g., Spear et al., 1998).

A third, less often addressed issue is the amount of handling (and, thus, possible stress) the rat pups and perhaps even pregnant dams undergo. Handling for experimental manipulations such as cocaine administration may involve a level of stress not controlled for in the experimental design, and early stressful conditions do alter response to a variety of challenge paradigms (e.g., Henry, Kabbaj, Simon, Le Moal, & Maccari, 1994; Meaney, Aitken, Viau, Sharma, & Sarrieau, 1989). Cross-fostering to untreated dams in prenatal exposure models is a related issue to environmental context, for there may be residual effects of cocaine exposure during pregnancy on maternal behavior (Goodwin, Heyser, Moody,

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Rajachandran, Molina, Arnold, McKinzie, Spear, & Spear, 1992). Finally, puberty may add another factor in the interpretation of cocaine-related effects for prenatal exposures, preweaning exposures, or both. Most studies examine prepubertal animals, and the few who have examined older animals following earlier exposure report some shifts in behavioral and neurochemical profiles postadolescence (see, for example, the below discussion regarding changes in stress response between adult and preadolescent exposed animals; Spear et al., 1998). Gender differences in behavioral and neurochemical response to prenatal exposure have been reported (e.g., Dow–Edwards, 1989; Dow–Edwards, Freed, & Milhorat, 1988; Dow–Edwards, Freed Malen, & Hughes, 1993; Gilde & Dow–Edwards, 1994; Shi, Goeders, Irby, & Dow–Edwards, 1998), though little systematic work has been done to date on the mechanism for such differences and for changes with puberty. For example, estrogen may be influential in aspects of the genetic expression of enkephalin, a neuropeptide involved in D_2 dopaminergic receptor systems that are potentially critical to some of the behavioral profiles observed in cocaine-exposed animals (see below; Zhu & Pfaff, 1995).

Cocaine-related effects on early gestational neuronal proliferation and migration

Growing evidence is available for cocaine-related effects on the earliest phases of cell proliferation and neuronal migration—and, thus, on cortical morphology. At the stage on neuronal formation and proliferation in cultured preparations of glioblastoma and neocortical cells, cocaine exposure delays uridine and thymidine incorporation (Garg, Turndorf, & Bansinath, 1993). Similarly, in cultured preparations, differentiation of neuroblastoma cells by nerve growth factor (NGF) and cell proliferation stimulated by insulinlike growth factor (IGF-I) are both delayed by cocaine (Zachor, Cherkes, Fay, & Ocrant, 1994). Prenatal exposure in the intact pregnancy with rats early in gestation interferes with radial gliogenesis and thus disrupts neuronal migration and resulting cortical architecture (Akbari, Whitaker–Azmitia, & Azmitia, 1994; Gressens, Gofflot, Van Meale–Fabry, Misson, Gadisseux, Evard, & Picard, 1992; Gressens, Kosofsky, & Evrard, 1992; Yablonsky–Alter, Gleser, Carter, & Juvan, 1992). In rhesus monkeys, intermittent prenatal cocaine exposure results in cerebral cortices with highly abnormal structural characteristics including disrupted cortical laminar architecture with an increased number of cells in the underlying white matter consistent with markedly impaired neuronal migration (Lidow, 1995). Many cortical cells do not reach their proper destination, and there is a decrease in the density of cortical glial (connective) elements. Mice embryos exposed to cocaine very early in gestation also show a decrease in glial formation, glial density, and a disorganization of axon–dendrite bundles (Gressens et al., 1992). Findings such as these may reflect disrupted monoaminergic-system-regulated processes that control the genesis of radial glial cells necessary for proper neuronal migration to cortical layers and regulate the formation of connections among neurons (Lidow & Rakic, 1994, 1995; Seidler, Temple, McCook, & Slotkin, 1995).

In addition to the effects of cocaine on monoaminergic regulated glial cell formation and maturation, cocaine may have a direct toxic effect on early stages of neuronal proliferation and also early connectivity, as suggested by cell culture preparations of both glia and neurons. With cocaine exposure to growing neurons in culture, there is a decrease in the number of neurons and a degeneration of the connective processes through which communication with other neurons occurs (Nassogne, Evrard, & Courtoy, 1995, 1998). There is no apparent reduction in glial cell numbers but there is also a change in structure suggesting again a cocaine-related effect on the morphology of cells involved in neural connectivity. Closer examination of cocaine-exposed neurons show morphologic changes in nuclei indicative of apoptosis or neuronal death after approximately 2 days of exposure, suggesting that cocaine exposure initiates apoptotic processes within the neuron by yet undefined mechanisms (Nassogne, Louahed, Evrard, & Courtoy, 1997). One possibility may be

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through monoamines, since in neuronal cell cultures exposure to catecholamines can lead to neuronal death through action as a glutamate agonist (Nassogne et al., 1998).

Direct effects on monoamine function

Several neurochemical effects have been reported in both in vivo and in vitro models, each pointing to prenatal cocaine-exposure-related effects on monoaminergic system development at the level of transmitter synthesis, activity, or receptor formation–function. The majority of studies have examined dopamine and serotonin systems.

Dopamine. Adult rats exposed prenatally to cocaine show a reduction in basal dopamine release and decreased activity in dopaminergic cells in the substantia nigra and ventral tegmentum (Minabe, Ashby, Heyser, Spear, & Wang, 1992). Reductions in glucose metabolic activity are particularly marked in prenatally exposed male rats in the hypothalamus, nigrostriatal pathway, and structures within the limbic system (Dow–Edwards et al., 1993). Prenatally exposed rabbits show reduced striatal dopamine levels at birth (Weese–Mayer et al., 1993), and rhesus at 60 days prenatally show reduced tyrosine hydroxylase mRNA (Ronnekleiv & Naylor, 1995) in the substantia nigra and ventral tegmental area.

A reduction in dopamine synthesis may lead to increased receptor sensitivity and proliferation, which is the case in both the prenatally exposed rhesus and rat (Dow–Edwards et al., 1993; Ronnekleiv, Fang, Choi, & Chai, 1998; Scalzo, Ali, Frambes, & Spear, 1990). Other studies examining receptor sensitivity and density following prenatal exposure have examined postnatal brains following early or late exposure and have reported conflicting results with either a decrease, no change, or an increase in the expression of D_1 and D_2 receptors and ligand binding to those receptors (Henderson, McConnaughey, & McMillen, 1991; Leslie, Robertson, Jung, Liebermann, & Bennett, 1994; Scalzo et al., 1990; Wang, Yeung, & Friedman, 1995). These conflicting results may reflect compensatory changes in dopamine neural transmission following withdrawal from cocaine or cessation of exposure, a suggestion that has been confirmed in adult animals (Bonci & Williams, 1996).

When cocaine is administered postnatally to rat pups in either the 1st or 2nd week postnatally (equivalent to later gestation in the human and during a period of rapid synaptogenesis), there is widespread increase in glucose metabolic activity across several different regions of the brain, including cortex (Dow–Edwards et al., 1993), but with particular increases in highly dopaminergic innervated regions. These effects are most dramatic in the female. For the male, there are no substantial areas of increased metabolism, and the nucleus accumbens continues to show decreased activity as was true prenatally. When ligands specific for dopamine D_1 and D_2 receptors are injected into postnatally treated animals, areas showing marked increase in glucose uptake are those with greater dopaminergic activity (Dow–Edwards, 1989). Earlier postnatal exposure (Days 1–10) affects the mesolimbic dopamine system and other structures within the limbic system differentially more than later postnatal exposure (Days 11–20), which results in more general activation (Dow–Edwards et al., 1988). Such general activation consistent with the relation between monoamines and synaptic formation suggests that exposure to a monoaminergic agonist such as cocaine during these periods of cortical maturation results in an overall increase in monoaminergic (and specifically dopaminergic) activity. How these findings would change if prenatally exposed animals were also exposed postnatally has not yet been examined.

More specific studies of receptor functioning have shown that prenatal cocaine exposure is associated with a functional decoupling of the D_1 receptor from G protein (Friedman et al., 1998; Wang et al., 1995), the second messenger within the cell that begins a cascade of intracelluar events. How this functional decoupling occurs as a result of cocaine exposure is not yet clear, nor has there been sufficient work to define a critical exposure period for that decoupling. Nonetheless, the effect appears specific to the striatal dopa-

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minergic system and to the D_1 receptor and to related cortical regions. For example, reduction in D_1 receptor-G protein coupling also occurs in the cingulate cortex in prenatally exposed animals (Friedman et al., 1996; Wang et al., 1995). Also, mRNA for the dopamine transporter are reduced in these same regions following both prenatal and postnatal exposure (Dow–Edwards et al., 1997; Leslie et al., 1994). Uncoupling the D_1 receptor from its second messenger systems dampens D_1-mediated responses within striatal neurons and within the cingulate cortex regulated functions. Behavioral responses to agonists selective for the D_1 receptor are reduced following both prenatal and postnatal exposure (Gilde & Dow–Edwards, 1994). Similarly, differential reduction in cingulate activity in cocaine-exposed animals is associated with an impaired ability to discriminate among salient or relevant stimuli (Gabriel & Taylor, 1998; Romano & Harvey, 1998). Efferent neurons from the striatum to the substantia nigra in the midbrain are predominantly D_1 receptors and contain several messenger neuropeptide systems, including dynorphin and substance P (Gerfen, Engber, Mahan, Susel, Chase, Monsma, & Sibley, 1990). Genetic markers (mRNA) encoding for dynorphin synthesis are markedly decreased in the nucleus accumbens following postnatal exposure (Dow–Edwards & Hurd, in press), the same region that showed persistent decrease in metabolic activity for males across both prenatal and postnatal exposure.

Taken as a group, these findings suggest a selective or at least a more specific attenuating effect of cocaine on the development of the D_1 system. In the normal individual, D_1 and D_2 receptor systems function interactively and in some ways reciprocally to regulate thalamic and cortical inputs. In particular, a reciprocal relation between D_1 and D_2 activity coupled also with a balance between noradrenergic α_2 and α_1 activity regulates and protects prefrontal cortical activity during increasing arousal or stressful states (see also above; Arnsten, 1997, 1998). Increased D_2 (and α_1) (Arnsten & Jentsch, 1997) activity may in effect take certain prefrontal cortical activities off-line and in effect interfere with aspects of attention and other higher order reasoning and discriminative abilities (functions that typically also deteriorate in hyperaroused states; see also above). An increase in D_2 activity might be expected to parallel attenuation in D_1 systems, and, indeed, prenatal cocaine exposure does appear associated with an increase in D_2 binding affinity, receptor density, and mRNA for the D_2 receptor in the striatum (Leslie et al., 1994; Moody, Frambes, & Spear, 1992; Stadlin, Choi, Tsim, & Tsang, 1995). Postnatal exposure (Days 1–9) also results in an increased density of D_2 in striatum (Howard et al., 1997). Additionally, challenges to the D_2 system using a D_2 antagonist, haloperidol, result in an exaggerated response in postnatally exposed male rats (Dow–Edwards, Shi, Yin, & Frick, 1998).

The behavioral implications of functional decoupling of the D_1 system may also be inferred in part from studies of D_1-deficient animals. D_1-deficient mice do not show the usual increase in locomotor behavior on cocaine challenge (Drago, Gerfen, Westphal, & Steiner, 1996; Xu, Hu, Cooper, Moratella, Graybiel, White, & Tonegawa, 1994), an observation perhaps consistent with the reduced response of pre- and postnatal cocaine-exposed rabbit and rat respectively to amphetamine challenge (Hughes, Pringle, Scribani, & Dow–Edwards, 1991). D_1-deficient mice also show reduced rearing behavior, a complex motor activity that is an essential part of an exploratory repertoire (Drago et al., 1996) and the reduction of which is similar to behavioral patterns seen in prenatally exposed animals (see below).

Serotonin. In relation to serotonin, in the developing brain cocaine appears to have greater affinity for the serotonin transporter—in contrast to the adult brain, in which cocaine binds predominantly to dopamine transporters (Shearman & Collins, 1996). Effects such as these have led several to suggest that in the developing brain the relationship between cocaine and serotonin systems may be more important to understanding mechanisms for teratogenic effects, while in the mature brain, and perhaps in the postnatal brain, dopamine systems may be more critical (Henderson et al., 1991). While less work has been done to date on serotonin systems and cocaine expo-

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sure, the findings are nonetheless consistent with hypotheses based on serotonin as an early trophic factor and cocaine-related effects on serotonin metabolism.

During development, serotonin neurons use a negative feedback mechanism for regulating growth. Both tissue culture and whole animal studies show that early in development increased extracellular serotonin causes a decrease in serotonin neuronal outgrowth. It has been demonstrated that early on cocaine inhibits the development of reuptake mechanisms (DeGeorge, Hochberg, Murphy, & Azmitia, 1989). Thus, based on cocaine's effect on synaptic reuptake, more serotonin should be present extracellularly in the synaptic cleft and thus reduce the growth of serotonin terminals (Whitaker–Azmitia, 1998). These predictions have been supported. Studies of prenatally exposed rats have revealed a decrease in the serotonin terminal density and an accompanying reduction in the normal growth of serotonin fibers in the hippocampus. The effect is transient, however, and by a month postnatally no differences between exposed and nonexposed animals are apparent (Akbari, Kramer, Whitaker–Azmitia, Spear, & Azmitia, 1992). On the other hand, by a month postnatally late-onset increased growth of serotonin fibers is observed in the striatum (Snyder–Keller & Keller, 1993). It may be that if growth is inhibited or delayed in one region, it is increased elsewhere (Whitaker–Azmitia, 1998).

But what about the return to normal by a month postnatally of serotonin fiber density in cortex and hippocampus? Rather than suggesting transient to no effect of cocaine, even early, brief disruption of one aspect of serotonin system ontogeny may disrupt other areas of the serotonin system development. Delayed serotonin terminal development may lead to decreased serotonin levels in later phases even after exposure has stopped. Decreased serotonin levels in the later prenatal and early postnatal period may have marked consequences for neuronal connectivity. For example, depletion of serotonin by selective synthesis inhibitors results in delayed neuronal differentiation and decreased synaptic connectivity in both cortex and hippocampus in the chick model (Cheng, Hamaguchi, Ogawa, Hamada, & Okado, 1993). In rats, depletion of serotonin on the postnatal Day 3 by a selective neurotoxin results in decreased density of granule cells dendritic spines or decreased connectivity which actually continues to worsen as the animals mature (Yan, Wilson, & Haring, 1997). Depletion at postnatal Days 10–20 causes marked loss in dendrites, with reductions still apparent up to a year of age (Mazer, Muneyyirci, Taheny, Raio, Borella, & Whitaker–Azmitia, 1997). Moreover, delaying serotonin terminal development has been associated with behavioral deficits in the adult animal (Shemer, Azmitia, & Whitaker–Azmitia, 1991). In other words, by altering serotonin terminal development, prenatal exposure alters events weeks downstream from the exposure.

In the first weeks postnatally in the rat, serotonin is required for astroglial maturation, and in the 2nd to 3rd postnatal weeks serotonin plays a critical role in neuronal maturation and synaptogenesis (Chubakov, Tsyganova, & Sarkisova, 1993). Postnatal synaptogenesis and neuronal connectivity depend on the maturation of a number of cell types including astroglial cells. Astroglial cells that play a role early in gestation as the radial glial cells for neuronal migration are also crucial for later connectivity and the production of neural growth factors. Serotonin has a regulatory role in the maturation of the astroglial cell (Lauder & Liu, 1994; Whitaker–Azmitia & Azmitia, 1994), and the rapid increase of serotonin 1A receptors ($5\text{-}HT_{1A}$) early in gestation in mammalian brain is largely through serotonin receptors on astroglial cells (Hellendall, Schambra, Liu, Breese, Millhorn, & Lauder, 1992). One aspect of that maturation is a morphologic change from the long processes needed for guiding neuronal migration to shorter but more processes with greater connectivity among cells. A second aspect of serotonin-mediated astroglial maturation is the release of growth factor S-100β (Whitaker–Azmitia, Murphy, & Azmitia, 1990). This particular growth factor causes neuronal outgrowth and neuronal plasticity in response to experience (such as activity, handling, enriched stimulation environments;

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Muller, Akhavan, & Bette, 1993; Whitaker–Azmitia et al., 1994). Thus, S-100β may be one factor involved in potentiation of learning and experience-dependent synaptogenesis. Depletion or decrease in S-100β release from astroglial cells should result in decreased dendritic development and delayed neural outgrowth.

Thus, prenatal cocaine exposure may interfere with astroglial cell maturation and in the release of S-100β. Prenatally exposed rat pups examined on postnatal Day 6 show a delay in the morphologic change in astroglial cells from their radial glial function to more mature cells (Clarke, Clarke, Muneyyirci, Azmitia, & Whitaker–Azmitia, 1996). There are also fewer astroglial cells in the cortex and hippocampal regions with overall cortical thinning. (Similar reductions in cortical astroglial cells have also been reported for the rhesus model at 2 months postnatal age [Lidow, 1995].) Immunochemical staining for S-100β revealed significant reductions (Akbari et al., 1994; Clarke et al., 1996). It is possible then that even if serotonin levels returned to normal in the subsequent postnatal period, the reduction of S-100β during that critical period may have more enduring effects. Conversely, treatment of prenatally exposed rat pups with 5-HT_{1a} agonists on postnatal Days 1 through 5 showed increases in S-100β in both cortex and hippocampus and a significant increase in brain growth (Akbari et al., 1994). Prenatal cocaine-exposure-associated delay in serotonin terminal growth, delay in astroglial maturation, and release of S-100β may lead to loss of synapses in the adult animal and thus to deficits in learning and memory (Whitaker–Azmitia, 1998).

In contrast to prenatal exposure, postnatal or preweaning exposure appears to increase serotonin levels. Postnatal exposure to serotonin agonists in the rat from birth to postnatal Day 20 increases brain activity during active synaptogenesis, leading to accelerated brain maturation (and behavioral changes in the mature animal, including increased anxiety and activity; Borella, Bindra, & Whitaker–Azmitia, 1997; Whitaker–Azmitia, 1998). In addition, preweaning cocaine administration decreases 5-HT_{1a} receptor density in the raphe nuclei (Dow–Edwards, 1998; Shi et al., 1998), where the action of the 5-HT_{1a} is inhibitory. Thus, decrease in receptor density is in effect an increase in afferent or ascending serotonergic activity (Pennington, Kelly, & Fox, 1991). No models to date have combined prenatal and preweaning exposure.

Serotonin neurons innervating the forebrain region also send projections to the hypothalamus and mediate changes in plasma ACTH, corticosterone, renin, and prolactin (Van de Kar, Richardson–Morton, & Rittenhouse, 1991). Disruptions in serotonin system ontogeny in both receptor distribution and density of serotonin projections may also alter hypothalamic response to neuroendocrine challenge tests. Adult rats treated prenatally between Day 13 and Day 20 of gestation and studied at postnatal Day 30 show increased ACTH and renin response to a serotonin receptor (5-HT_{1A}) agonist (Battaglia & Cabrera, 1994; Battaglia, Cabrera–Vera, Van De Kar, Garcia, Vicentic, & Pinto, 1998). In contrast, ACTH and renin response is attenuated to a serotonin releaser acting at the presynapse. These changes in response to neuroendocrine challenge are not paralleled by changes in 5-HT_{1A} receptor density in hypothalamus or midbrain or by any alteration in serotonin uptake sites at the presynapse or in levels of serotonin. However, by postnatal Day 70, 5-HT_{1A} receptor density is increased in cortex and midbrain but not hypothalamus (Cabrera, Yracheta, Li, Levy, Van de Kar, & Battaglia, 1993), findings that speak to ongoing alterations in monoamine-related systems after exposure has ceased and the alteration of effects downstream after early changes in system function. Furthermore, findings such as these also suggest that certain alterations in monoaminergic system function related to prenatal cocaine exposure may be only apparent when systems are challenged.

Norepinephrine. Far fewer studies have been done on the relation between prenatal cocaine exposure and the developing noradrenergic system, and the majority have been in the postnatal but preweaning period. Preweaning cocaine administration appears to increase activity within the overall noradrenergic system

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(Seidler & Slotkin, 1992). Also demonstrated has been increased fiber density in norepinephrine-rich regions, increased receptor binding (β_1 in cortex at 30 days postnatal but not later; α_1 and α_2 in cerebellum and forebrain), and increased presynaptic synthesis of norepinephrine (Akbari & Azmitia, 1992; Henderson et al., 1991; Seidler & Slotlain, 1992). Rat pups exposed to cocaine on postnatal Days 4–9 and then exposed to a noradrenergic agonist (clonidine) showed enhanced response to the locomotor stimulating effects of the agonist (Barron, Staton, Willford, & Hansen–Trench, 1998).

Noradrenergic neurons arising from the locus coeruleus innervate the entire forebrain with many projections to the posterior and prefrontal cortex. The locus coeruleus appears critical to vigilance or the response to a salient target (Delagrange, Canu, Rougeul, Buser, & Bouyer, 1993), possibly through projections to the prefrontal cortex. Of special significance is the afferent input from the prefrontal cortex to the locus coeruleus that suggests a feedback, modulating link between cortical activity and ongoing noradrenergic activity (Arnsten & Goldman–Rakic, 1984). Excessive stimulation of adrenergic α_1 receptors in effect take the prefrontal cortex offline (Arnsten & Jentsch, 1997). This in turn disrupts the regulatory loop between the locus coeruleus and the prefrontal cortex and may disrupt the capacity for vigilance and the ability to distinguish salient from nonsalient information (Rajkowsi, Kubiak, Ivanova, & Aston–Jones, 1998), a behavioral finding in cocaine-exposed animal models (Gabriel & Taylor, 1998; Romano et al., 1998) and suggested in human studies (Mayes, Bornstein, Chawarska, Haynes, & Granger, 1996; Mayes et al., 1998). These findings underscore the importance for more preclinical work to examine cocaine-related effects on noradrenergic system ontogeny.

In Utero Cocaine Exposure and Immediate Early Genes

In the mature brain exposed chronically to cocaine (and other drugs of abuse), neuronal functions gradually change (e.g., tolerance) and these changes may endure even after cessation of drug use. Such delayed, gradually developing, and persistent changes in function suggest that a candidate mechanism for addictive phenomena may be long-term changes in neuronal gene expression (Nestler, Bergson, Gultart, & Hope, 1993). Similarly, in the developing brain, changes that persist beyond the acute prenatal or preweaning exposure as described above (e.g., changes in receptor density, expressions of neural growth factors, connecting fiber density) suggest alterations in the genetic programs for ongoing neural function and development.

In the mature brain, genes regulate the synthesis of neuropeptides, monoamines, their receptors, transporters, second messengers, and so on. The expression of specific genes in the central nervous system appears regulated by a class of DNA-binding proteins termed transcription factors. These transcription factors bind to the regulatory regions of certain genes and affect the rate at which these genes are transcribed (and thus the synthesis of the relevant synaptic components). These transcription factors, called as a group *immediate early genes* (IEGs; Sheng & Greenberg, 1990), appear rapidly (within minutes) in response to neuronal stimulation. The mRNAs transcribed from IEGs often have a very short half-life (i.e., the induction of these genes is short-lived). For example, the IEG c-*fos* can be undetectable within a 0.5 hr of stimulus induction (Sheng et al., 1990). For the induction of c-*fos*, c-*jun*, and *zif*/268 in response to novel stimulation, mRNA transcription occurs within 5 min, with peak steady-state levels of mRNA at 30–45 min and peak protein synthesis within 2 hr of stimulation (Kosofsky & Hyman, 1993). IEGs may activate or repress the rate at which other genes are transcribed, though the mechanism for this regulation of transcription rate is not yet clear (Plashne & Gann, 1990). The transient nature of the mRNAs from induction of IEGs suggest a complicated stimulus-dependent mechanism for regulating such events as the synthesis of receptors and transporters. The IEG response can also be used as a marker of neuronal activation (Sheng et al., 1990) and provides information complementary to that of regional glu-

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cose metabolism, which predominantly labels nerve terminals activated by a stimulus or drug.

Drugs of abuse affect the expression of IEGs in the mature and the developing animal, and the effect is apparent during and after treatment. This relation may be one mechanism to explain how substances of abuse alter genetic programs in the different phases of neural ontogeny. That is, drug-induced alterations in IEG expression can modify neural gene expression during development and thereby alter, perhaps permanently, cellular identity and neuronal repertoire (Kosofsky et al., 1993). In the adult animal, exposure to cocaine enhances the expression of several IEGs including c-*fos and zif*/268 as well as genes encoding for neuropeptides substance P and dynorphin involved in the predominantly D_1 striatonigral dopaminergic pathways (Steiner & Gerfen, 1993, 1995). Similar induction of these same IEGs is seen with D_1 agonists (Robertson, Vincent, & Fibiger, 1992). The cocaine-related induction can be blocked with D_1 antagonists (Steiner & Gerfen, 1995) and does not occur in a D_1-deficient mouse (Drago et al., 1996; Moratella, Xu, Tonegawa, & Graybiel, 1996). The cocaine-related effect on the serotonin system (but not the norepinephrine system) also seems related to induction of c-*fos* and *zif*/268 (Bhat & Baraban, 1993). Similarly, with chronic exposure there may be long-term perturbations in IEG expression. For example, during withdrawal from cocaine treatment adult rats showed reduction in c-*fos* expression for several days (Ennulat, Babb, & Cohen, 1994).

In the preweaning exposure model, beginning lines of work point to cocaine-related induction of IEG expression following neural stimulation particularly in the striatum D_1 rich regions (Kosofsky, Genova, & Hyman, 1994; Kosofsky et al., 1995a,b; Kosofsky & Hyman, 1993). On postnatal Day 8, induction of c-*fos* and *zif*/268 occurs primarily in the striatum, but by Day 15 induction of both occurs in striatum and cortex at the same time corticostriatal connections are rapidly forming (Kosofsky et al., 1995a,b). The candidate target genes whose expression may be altered by cocaine-related induction of these IEGs include those involved in growth factor synthesis, neuropeptide precursors, and monoamine synthesis; and the present challenge is to identify the target genes for the IEGs in the developing brain (Nestler et al., 1997). Mistimed induction of IEGs with the subsequent alteration of the expression of a cascade of related genes may have continued effects on the genetically coordinated development of neural circuitry. It also may be that long-term exposure as is the case in the human model may alter the relation between stimulation and IEG expression such that IEGs are either over- or underexpressed with stimulation long after exposure has ceased. Such a possibility would have profound implications for ongoing neural development during the synaptogenic phase. These are lines of work yet to be extensively pursued.

Neurobehavioral Correlates

Several laboratories are studying neurobehavioral correlates of the alterations in monoaminergic function outlined above. Some neurobehavioral changes are apparent in prepubertal animals and apparently disappear by adulthood, others persist, and a few appear later in development. In this context, it is important to highlight two general principles. First, the central nervous system continues to develop after the cessation of exposure. Acute differences in neurobiological function and behavior may endure or attenuate with ongoing neural development. Second, compensatory processes are pervasive in central nervous system development. Without these continual microadjustments and compensations that occur during normal neural ontogeny, more functional impairments and developmental failures might occur than is indeed the case. With early drug exposures, these same compensatory mechanisms may promote substantial realignment or correction within other neural systems to allow for the return of some functions (see, e.g., the hypothesis above regarding the reciprocal relation between the D_1 and D_2 systems). These compensations may not be without costs and may not restore the organism to average or

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fully functional state. Indeed, it may be that such neural compensations stabilize functioning under basal conditions, but with stress or challenge continued deficits may be most apparent (Spear, 1997; Spear et al., 1998).

The neurobehavioral areas most frequently studied are (a) locomotor behavior in open field exploration and responses to monoaminergic agonists and antagonists, (b) attention and conditioned learning, and (c) stress reactivity. In each of these areas, a pattern of neurobehavioral correlates has emerged. Several laboratories studying cocaine and monoaminergic function in the rat, mouse, or rabbit are also examining related behavioral alterations in those domains of behavior most likely related to alterations of mesolimbic or nigrostriatal systems. These include changes in locomotor behavior and in attention. The findings regarding locomotion are mixed, depending on the assessment paradigm, the exposure period, and the time of assessment. Prenatal exposure appears to increase spontaneous locomotor activity in open-field exploration during the first 3 weeks of life but not by 60 days of age (Henderson & McMillen, 1990). Others have reported the same lack of relation between prenatal exposure and locomotor activity after the first weeks of life (e.g., Peris, Coleman, & Millard, 1992; Riley & Foss, 1991a,b). Female rats treated on postnatal Days 1–10 and studied between 60 and 65 days of age show decreased levels of activity (Dow–Edwards, 1989). Prenatally exposed animals also inhibit approaching novel conditions and open-field exploration (Johns, Means, Anderson, Means, & McMillen, 1992), and wall-climbing behavior, a dopaminergic regulated behavior, is attenuated with foot shock in prenatally exposed animals (Spear, Kirstein, Bell, Yoottanasumpun, Greenbaum, O'Shea, Hoffman, & Spear, 1989). Exposure on postnatal Days 11–20 reduced the locomotor response to amphetamine challenge in rats (Hughes et al., 1991). Similarly, amphetamine challenge in prenatally exposed rabbits failed to elicit a stereotypic head bobbing, usually associated with activation of the D_1 receptor, and this effect persisted through adulthood (Levitt, Harvey, Friedman, Simansky, & Murphy, 1997).

The aforementioned hypothesis regarding the uncoupling of the D_1 receptor rendering it dysfunctional has some support in related behavioral studies. D_1 receptor activation regulates the increased locomotor response to cocaine (Cabib, Castellano, Cestari, Filibeck, & Puglisi–Allegra, 1991). Reduced D_1 activity would be expected to reduce behaviors usually stimulated by dopamine agonists, especially selective D_1 agonists. D_1 deficient mice do not show the usual increase in locomotor behavior on cocaine challenge (Drago et al., 1996; Xu et al., 1994), an observation perhaps consistent with the reduced response of pre- and postnatal cocaine-exposed rabbit and rat respectively to amphetamine challenge (see above; Hughes et al., 1991). D_1-deficient mice also show reduced rearing behavior, a complex motor activity that is an essential part of an exploratory repertoire (Drago et al., 1996). While other motor behaviors are variously altered in D_1-deficient mice (including overall activity level, grooming, and sniffing; Xu et al., 1994), rearing may be a more sensitive behavioral marker of D_1 receptor dysfunction (Drago et al., 1996). Also, studies of locomotor response to novelty suggest that high-responding animals show greater D_1 binding in the nucleus accumbens and less D_2 binding in both accumbens and striatum (Hooks, Juncos, Justice, Meiergerd, Povlock, & Schenk, 1994), again a possible parallel with the reduced open-field exploration behaviors of cocaine-exposed animals (see above).

Deficits in learning are suggested by impairments in classical conditioning (Heyser, Chen, Miller, Spear, & Spear, 1990; Spear et al., 1989), deficiencies in active and passive avoidance tasks (Heyser et al., 1990), increased response perseveration (Smith, Mattran, Kurkjian, & Kurtz, 1989), diminished proximal cue learning (Vorhees, Reed, Acuff–Smith, Schilling, Cappon, Fisher, & Pu, 1995), and impaired habituation (Heyser, McKinzie, Athalie, Spear, & Spear, 1994). This collection of findings cuts across prenatal and preweaning exposure. There may also be evidence suggestive of a role for the D_1 uncoupling in the learning deficits. Prenatally exposed rabbits show pronounced anatomical changes in the anterior cingulate cortex (a

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richly dopaminergic region). Specifically, neurons in this region show marked increase in dendrite outgrowth (Levitt et al., 1997), a deficit possibly connected to the decoupling of the D_1 receptor inasmuch as D_1 receptor activation in normal animals decreases dendritic outgrowth (Reinoso, Undie, & Levitt, 1996). Indeed, D_1 receptor-G protein coupling has been shown reduced in the cingulate cortex in prenatally exposed animals (see also previous sections; Friedman et al., 1996; Wang et al., 1995).

Also, lesions in the anterior cingulate cortex impair attentional processes, and in intact animals attentional tasks lead to activation of this region (Vogt & Gabriel, 1993). Prenatally cocaine-exposed rabbits with changes in the anterior cingulate region show reduced learning ability when the positive conditioning stimulus less salient than the negative stimulus (e.g., a soft tone vs. a loud tone; Levitt et al., 1997; Romano et al., 1998). In other words, these animals cannot attend preferentially to less salient but relevant stimuli in the context of more salient background (and irrelevant) stimuli. These deficits persisted into adulthood (Romano et al., 1998). Other studies have also suggested an association between prenatal cocaine exposure and impaired attentional processes that impede the animal's ability to change previously learned conditions or to screen out distracting but nonrelevant information (e.g., Heyser, Spear, & Spear, 1992; Kosofsky & Wilkins, 1998).

Altered stress responsivity is suggested by several behavioral observations and is the domain most relevant to the earlier suggestion that early compensatory mechanisms which "normalize" basal conditions may nonetheless leave the adult animal with a vulnerability to novel, challenging, or stressful contexts (Spear et al., 1998). While neural "stress circuitry" is complex and involves many interactive systems, including the corticosteroid based HPA axis, dopaminergic and noradrenergic pathways in the amygdala and other limbic and corticothalamic systems are central (Dunn & Kramarcy, 1984). Furthermore, stress selectively stimulates many of the same dopaminergic regions as does cocaine. Prenatally exposed rats, while initially showing less motor response to open-field exploration, do engage in exploration after a delay and then do so with markedly increased activity, suggesting overarousal (Henderson et al., 1991; Hutchings, Fico, & Dow–Edwards, 1989; Spear, Frambes, & Kirstein, 1989). Similarly, adult rats exposed to cocaine prenatally demonstrate less expected stress-induced immobility during a forced swim, intermittent foot shock, or when placed in a novel condition following foot shock (Bilitzke & Church, 1992; McMillen, Johns, Bass, & Means, 1991; Molina, Wagner, & Spear, 1994; Smith et al., 1989; Spear et al., 1989, 1998). This alteration in stress responsivity as manifest by immobility changes with age. Prepubertal or preweaning animals exposed prenatally to cocaine show greater immobility in stressful conditions such as forced swim or foot shock (Goodwin, Bliven, Kuhn, Francis, & Spear, 1997; Molina et al., 1994; Wood, Molina, Wagner, & Spear, 1995). Other behaviors suggest increased arousal and altered stress responsivity. Prenatally exposed animals are more sensitive to environmental demands and show more aggression than nontreated animals in conditions of water deprivation and competition for water (Spear et al., 1998; Wood & Spear, 1998). Increased aggression is not apparent, however, if the animals are not stressed (Spear et al., 1998). Far more work is required to link these behavioral observations of altered stress responsivity with the alterations in neurochemical function related to prenatal cocaine exposure.

Finally, there is some suggestion that prenatally cocaine-exposed animals may be more sensitive to the effects of early experience (stressful and nonstressful). With chronic stress (such as repeated foot shock over time), preadolescent cocaine-exposed animals "reverse" their acute stressor pattern of reduced immobility and show more immobility than is expected in nonexposed animals (Goodwin et al., 1997). Nonexposed but repeatedly stressed animals show less significant changes in the pattern of their stress response. Findings such as these about the effects of "early experience" point to potentially productive lines of work using more traditional early experiences, such as increased handling, that

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have been studied in relation to adrenocortical function and stress (Meaney et al., 1989; Spear et al., 1998).

Findings in Infants and Preschool Aged Children

Neurochemical findings in infants and children

In human infants, neurochemical studies following prenatal exposure are to date scant, but two areas of work point to effects on those neurochemical systems most related to arousal regulation and altered response to stress. Three studies have examined metabolites, precursors, or levels of norepinephrine or dopamine in the serum or cerebrospinal fluid of newborns exposed to cocaine prenatally and have found a significant increase in plasma norepinephrine (Ward, Schuetz, Wachsman, Bean, Bautista, Buckley, Sehgal, & Warburton, 1991) and catecholamine precursors in CSF (Mirochnick, Meyer, Cole, Herren, & Zuckerman, 1991) and a decrease in the metabolites of dopamine (Needlman, Zuckerman, Anderson, Mirochnick, & Cohen, 1993), findings suggesting an alteration in monoaminergic system function at least neonatally. Further, for the cocaine-exposed infants, norepinephrine levels were inversely related to features of the infant's neurobehavioral profile (Mirochnick et al., 1991). Second, cocaine-exposed infants exhibit an attenuated cortisol response to noninvasive (neurobehavioral exam) and invasive (heelstick) manipulations despite no differences in baseline cortisol levels (Mangano, Gardner, & Karmel, 1992), suggesting that glucocorticoid-mediated arousal regulatory systems are altered by in utero cocaine exposure or by the chronically stressful conditions associated with cocain exposure (Karmel, Gardner, & Magnano, 1991).

Neurobehavioral findings in infants and children

Impairments in the distribution of sleep states, startle response, brain-stem-evoked potential, overall neurological maturity, and cry characteristics indicative of delays in neurological maturation have been described in cocaine-exposed neonates (Anday, Cohen, Kelley, & Leitner, 1989; Chiriboga, Bateman, Brust, & Hauser, 1993; Corwin, Lester, Sepkoski, McLaughlin, Kayne, & Golub, 1992; Regaldo, Schechtman, Del Angel, & Bean, 1995; Shih, Cone–Wesson, & Reddix, 1988). In the areas of arousal, attention, and executive functioning (e.g., habituation, conditioned learning, novelty recognition), differences have been noted between cocaine-exposed and non-cocaine-exposed infants at least through the 2nd or 3rd year (Mayes et al., 1995). Struthers and Hansen (Hansen, Struthers, & Gospe, 1993; Struthers, & Hansen, 1992) reported impaired recognition memory among cocaine- or amphetamine-exposed infants compared to a non-drug-exposed group between 7 and 8 months of age. Similarly, Alessandri and colleagues (Alessandri, Sullivan, Imaizumi, & Lewis, 1993) reported delays in novelty responsiveness and conditioned responsiveness well into the second half of the 1st year of life. Others following infants through a year of age have demonstrated that despite faster reactivity or response time on a visual expectancy paradigm, cocaine-exposed infants show poorer recognition memory (most evident among the most heavily exposed group; Jacobson, Jacobson, Sokol, Martier, & Chiodo, 1996). Mayes and colleagues (Mayes, Bornstein, Chawarska, & Granger, 1995; Mayes et al., 1996) reported increased reactivity and irritability in response to novel stimulation among cocaine-exposed infants, and these differences occurred in the context of no differences on measures of infant information processing (e.g., rate of habituation). Impairments in arousal-modulated attention reported at 1–4 months of age describe cocaine-exposed infants not regulating their attention to more or less salient stimuli as their endogenous arousal states varied (e.g., before and after feeding; Freedland, Karmel, Gardner, & Lewkowicz, 1998; Karmel & Gardner, 1996; Karmel, Gardner, & Freedland, 1996). At 4 months of age in a still-face procedure, those infants more heavily exposed to cocaine recovered less readily following resumption of usual interactions (Bendersky

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& Lewis, 1998a,b). Azuma and colleagues (Azuma & Chasnoff, 1993) also report poor task persistence and increased irritability and distractibility among cocaine-exposed 3-year-olds participating in standardized testing. Others have also reported poor impulse control and emotional lability in frustrating situations between 2 and 3 years of age (Bendersky & Lewis, 1998a,b).

Summary

While far more work is needed at the preclinical level, findings are accumulating to suggest a targeted and enduring effect of prenatal cocaine exposure on monoaminergic system ontogeny and function. Early gestation exposure to cocaine may affect the most basic processes of neuronal proliferation and migration, while later exposure influences neuronal maturation and synaptogenesis. It is probable that there are differential effects on the three monoaminergic systems and that impairment in one system may be compensated for through up- or downregulation of another. This interactive and compensatory mechanism may account in part for variations in findings, depending on the age of the animal at the time of study. Combining prenatal and preweaning exposure models will be important to model the more common human condition of exposure throughout pregnancy. In addition, promising work suggests that with maturation some of the baseline behavioral effects of prenatal exposure may be less apparent, but deficits continue to be manifest under stressful or novel conditions. The preclinical models are extremely useful for suggesting hypothesis and potentially fruitful avenues of study in the human.

In summary, four lines of evidence suggest a plausible link between prenatal cocaine exposure and specific effects on the mechanisms subserving arousal and attention regulation in infants and preschool aged children. These are (a) the association of prenatal cocaine exposure with alterations in monoaminergic system ontogeny with suggestive findings, pointing to a functional decoupling of dopamine D_1–D_2 interaction, an increase in D_2 and norepinephrine activity, and a dysregulation of serotonin mediated neuronal connectivity and neural growth factors; (b) neurobehavioral effects of prenatal cocaine exposure in animals, including inhibited exploration and altered responses to stress, suggesting overarousal in the face of novel–stressful situations and disrupted attention and learning; (c) altered norepinephrine system function in cocaine-exposed human infants and altered glucocorticoid response, suggesting altered stress response systems; (d) neurobehavioral findings in infants and preschool-aged children suggestive of disrupted arousal regulation in the face of stress or novelty, increased distractibility, impulsivity, and consequent impaired attention to novel, structured tasks.

Cocaine or crack use continues at moderate to high rates among certain groups of pregnant women. In many inner-city populations, nearly 50% of women giving birth report or test positive for cocaine use at the time of delivery (Amaro, Fried, Cabral, & Zuckerman, 1990); thus, many infants continue to be born exposed in utero to cocaine and other drugs. How early deficits in arousal and attention regulation may be expressed later in children's cognitive development, learning, school performance, social functioning, capacity to metabolize stressful conditions, and psychiatric–psychological dysfunctions of attention (e.g., ADHD), anxiety, or conduct disorders is a long-term implication of the present study. Further, as prenatally cocaine-exposed children reach school age, the cumulative effects of the postnatal substance-abusing environment may account for a large portion of the variance in the child's developmental and psychological outcome.

Intervention Implications

There are at least three implications of the preclinical findings and the beginning parallels in human studies. First is the issue of compensatory processes after exposure has ended. While it is true that early neural events related to cocaine exposure do alter other ontogenetic events downstream long after exposure has ended, it is also true that for young children there is an enormously rapid, experi-

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ence-dependent phase of neural development in the first 3 to 4 years. Synaptic formation and synaptic remodeling are occurring at extraordinarily rapid rates during these early years, and the possibility for remodeling and compensation is surely present. Regretfully, many if not the majority of infants exposed to cocaine prenatally grow up in less than adequate environments that may not be able to provide the sufficient experiential substrate to facilitate neural compensatory processes. Rather, it may be that the very vulnerability to dysfunctional arousal systems is further compromised by the inadequate to chaotic environments that these children grow up in. Thus, one critical implication is not only that early intervention is necessary but also that interventions for these children must include their parents at all levels of care and substance-abuse treatment programs must conversely include intervention programs for the children. Family-based interventions need to be as comprehensive as the present state of the art allows and instituted as early as is feasible for a given service agency's context and resources. The tragic reality is there are usually markedly insufficient psychosocial services available for substance-using families and their children, and the design of available services does not always facilitate access by a severely addicted, often homeless and depressed substance-using parent.

A second intervention implication regards the continued vulnerability to arousal and attention regulatory difficulties that these children may continue to exhibit, especially as cognitive and social demands increase with entry into school. While the children may have difficulties with aspects of attention in school that are phenotypically similar to attention deficit disorder, the state of our knowledge is insufficient to make that parallel on a functional level. Clinical anecdotal data suggest that prenatally exposed children do not respond in the usual way to stimulants typically used for children with the profile most commonly labeled attention deficit disorder. Carefully designed and conducted psychopharmacologic studies are urgently needed in order to make more informed decisions regarding possible medication interventions for these children once they reach school age. Similarly, educational strategies are needed that address the children's lability, difficulty sorting salient from nonsalient, and tendency to become overwhelmed. At the same time, these strategies must not be stigmatizing or carry the implicit (or explicit) link to parental drug abuse. Attitudes toward substance use in adults carry over to their offspring and often dramatically influence teachers' (and other professionals') attitudes toward the children's abilities and potential (Thurman, Brobeil, Ducette, & Hurt, 1994). Designing special educational strategies requires sensitivity not only to the most sophisticated teaching techniques but also to the insidious effect of attitudes on children's performance.

The third implication for intervention pertains to the mental health needs of these children and their families. A combination of their prenatal and early postnatal experiences puts these children at considerable risk for poor adjustment and behavioral and psychiatric difficulties by school age. These include increased risk for depression, problems with conduct, attentional difficulties, and anxiety disorders. At the very least, the children of substance abusers are at increased risk for substance abuse themselves. Further, the risk for increased mental health problems reflects a complex interaction among neurologic vulnerabilities based on prenatal exposure, the effect of depriving or traumatic environments, and conveyed genetic risks. While any genetic basis for substance abuse is surely polygenic and any cluster of genes probably work in concert with environmental contexts to convey increased risk for substance abuse in only a *certain proportion* of substance users, for these families this same genetic risk is nonetheless conveyed to their children. Thus, as these children enter middle school and early adolescence they will need more attention from mental health professionals who can understand complex models of biology–gene–environment interaction. Mental health interventions informed by these models as well as by those of behavioral teratology and developmental psychopathology will be critical to breaking the continued cycle of substance use, poverty, and environmental chaos that so often tracks the lives of so many children from substance-using homes.

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