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Drugs, Biogenic Amine Targets and the Developing Brain

Aliya L. Frederick[a] Gregg D. Stanwood[b, c]

[a]Neuroscience Graduate Program, [b]Department of Pharmacology, and [c]Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, Tenn., USA

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Abstract
Defects in the development of the brain have a profound impact on mature brain functions and underlying psychopathology. Classical neurotransmitters and neuromodulators, such as dopamine, serotonin, norepinephrine, acetylcholine, glutamate and GABA, have pleiotropic effects during brain development. In other words, these molecules produce multiple diverse effects to serve as regulators of distinct cellular functions at different times in neurodevelopment. These systems are impacted upon by abuse of a variety of illicit drugs, neurotherapeutics and environmental contaminants. In this review, we describe the impact of drugs and chemicals on brain formation and function in animal models and in human populations, highlighting sensitive periods and effects that may not emerge until later in life.

Many Drugs of Abuse and Therapeutics Target Biogenic Amines

Biogenic amines are a group of neurotransmitters derived by the enzymatic decarboxylation of naturally occurring amino acids. These transmitters include the catecholamines, dopamine and norepinephrine, as well serotonin and acetylcholine. Each of these neurotransmitters has characteristic properties of synthesis, packaging, release, targets, degradation and action that allow its characterization at the synapse.

Biogenic amines are implicated in a wide range of behaviors, cognitive functions and homeostatic functions in the mature central nervous system (CNS). However, these neuromodulators appear early during embryogenesis, well before the onset of synaptogenesis, suggesting that they also play important roles in brain development. It is therefore not surprising that alterations to these systems, either by pharmacological agents that affect synthesis or binding in the mature system, or developmentally due to toxic insults or genetic modifications, will have important consequences on the brain. In this review, we will particularly emphasize the role of the developing dopamine system, but also describe data implicating noradrenergic and serotonergic projections. For discussion of other neurotransmitter systems and drug targets during development, we refer the reader elsewhere

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Gregg D. Stanwood, PhD
Vanderbilt Kennedy Center
23rd Ave South, 476 RRB
Nashville, TN 37232-6600 (USA)
Tel. +1 615 936 3861, Fax +1 615 936 2202, E-Mail gregg.stanwood@vanderbilt.edu

[Slotkin, 1998; Francis et al., 1999; Olney et al., 2002; Abreu-Villaca et al., 2003; Herlenius and Lagercrantz, 2004; Rodier, 2004; Holmes et al., 2005].

Dopamine

Dopamine (DA) is widely distributed in the adult CNS and serves a variety of functions in the mature brain, including control of movement. DA is also involved in regulation of the endocrine, limbic and cardiovascular systems. DA abnormalities appear to contribute to many neurological and psychiatric disorders, including schizophrenia, Parkinson's disease, attention-deficit hyperactivity disorder and drug addiction [Kiyatkin, 1995; Goldman-Rakic, 1998; Nestler, 2001; Girault and Greengard, 2004; Arnsten and Li, 2005; Biederman and Faraone, 2005; Kalivas and Volkow, 2005]. Many drugs used for therapeutic purposes, such as antipsychotics, act directly on the DA system.

All the catecholamines, characterized by a benzene ring with 2 hydroxyl groups and attached amine group, are derived from the amino acid tyrosine. DA is synthesized from conversion of L-tyrosine into L-dopa by the rate-limiting enzyme tyrosine hydroxylase. Subsequent activity of DOPA decarboxylase results in conversion to dopamine. DA receptors are characterized by an extracellular N-terminus region, intracellular C-terminus region and 7 membrane-spanning regions. The receptors are coupled intracellularly to guanine nucleotide-binding proteins that induce intracellular signaling cascades to influence regulation of calcium and potassium channels on the postsynaptic membrane. There are 2 subfamilies of DA receptors based on their pharmacological profiles and sequence homology: D_1-like receptors and D_2-like receptors. D_1-like receptors, including the D_1 and D_5 receptor subtypes, catalyze the synthesis of cyclic adenosine monophosphate (cAMP) from the action of adenylate cyclase on adenosine triphosphate. D_2-like receptors, including the D_2, D_3 and D_4 receptor subtypes, inhibit cAMP synthesis [Kebabian and Calne, 1979; Missale et al., 1998]. Transmitter action is terminated by re-uptake into the presynaptic terminal by a high-affinity plasma membrane dopamine transporter and ezymatically degraded by monoamine oxidase or catechol-*o*-methyl transferase.

There are several major dopaminergic pathways. The nigrostriatal tract consists of dopaminergic neurons in the substantia nigra pars compacta that terminate in the striatum, a major DA-containing area of the brain. The striatum is a component of the extrapyramidal motor system, and plays an essential role in the coordination of locomotor activity. Degeneration of the neurons in the nigrostriatal pathway is the primary pathological finding in Parkinson's disease, resulting in characteristic motor dysfunction. DA is also believed to be involved with the limbic system, particularly in behaviors associated with motivation, reward (endogenous systems and drug abuse) and reinforcement. The mesolimbic and mesocortical pathways are 2 midbrain dopaminergic pathways implicated in these behaviors. Both pathways begin in the midbrain ventral tegmental area (VTA) and provide input to the nucleus accumbens and frontal cortex (both medial prefrontal and anterior cingulate), respectively [Olson et al., 1972]. In monkeys, it has also been observed that a subset of VTA neurons provide innervation to the caudate nucleus of the striatum; thus, implicating the striatum in the regulation of emotional behaviors in this species [Lynd-Balta and Haber, 1994a, b; Haber et al., 1995].

Tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis and a useful marker for identifying DA neurons, is first apparent at embryonic days (ED) 12–13 of an approximate 21-day gestational period in the rat midbrain, and is present by ED 14 of an approximate 30-day gestational period in the rabbit. DA is also likely to have early biological activity in the primate brain. In the monkey, DA neurons of the substantia nigra /VTA are produced between ED 36 and ED 43 of a 165-day gestational period [Levitt and Rakic, 1982]. In humans, midbrain DA neurons appear during the first trimester in the second month of gestation [Olson and Seiger, 1972]. This input is thus already present in the cortex even while more superficial cortical layers (II–IV) are beginning to form, consistent with a morphogenic role of DA.

Axons of dopaminergic cells reach the cortex a few days after their initial detection in the midbrain, innervating the cortex in a bilaminar pattern with greatest input into layers II and/or III and V and/or VI depending upon the cortical region in the monkey. This stands in contrast with the innervation pattern in rodents, in which there is substantial innervation of layer I as well as overlap between thalamic and catecholamine neurons in layer IV [Levitt et al., 1984]. Limbic cortical regions, such as the anterior cingulate and medial prefrontal cingulate receive the densest dopaminergic innervation. The density of tyrosine hydroxylase-positive axons in the cortex increases gradually over development, then declines postnatally to reach adult levels during puberty. This protracted postnatal increase in dopamine content occurs over a time period during which a number of developmental milestones occur that may involve transmitter

signaling, including obtaining competency on working memory tasks [Lambe et al., 2000].

Fluorescent histochemical analysis of DA afferents in the cortex shows regional differences in DA input that correspond well with the heterogeneous distribution of endogenous DA content assayed biochemically in the cortex [Brown et al., 1979; Reader et al., 1989a]. In the monkey, in addition to dense prefrontal DA innervation, there is also substantial DA input to the premotor and primary motor cortex, as well as the anterior regions of the superior and inferior gyri of the temporal lobe. Minimal contributions of DA afferents, however, are found in the parietal and occipital lobes across species [Levitt et al., 1984; Reader et al., 1989a]. The mechanisms responsible for the proper guidance of dopaminergic afferents from the midbrain to the cortex and the morphogenic properties of these afferents on cortical neurons are not well-understood, but netrins and ephrins have been implicated [Yue et al., 1999; Flores et al., 2005; Lin and Isacson, 2006].

Transcripts for the D_1, D_2 and D_3 receptors can be detected in the striatum and cortex by ED 14 in the rat and by ED 12 in the mouse [Jung and Bennett 1996; Araki et al., 2007]. D_1 and D_2 receptors are measurable at these early prenatal time points, and increase in abundance throughout prenatal and early postnatal development to reach adult levels of expression between postnatal days (PD) 14 and 21 in rodents [Sales et al., 1989; Rao et al., 1991; Schambra et al., 1994; Caille et al., 1995]. In the monkey, DA receptors appear in target regions of DA input by the first quarter of gestation [Lidow et al., 1991; Lidow 1995a], and, in humans, DA receptor binding sites have been detected by week 12 of gestation [Aubert et al., 1997]. Therefore, in all species examined, DA receptors are present very early in prenatal development, consistent with a role for DA in regulating neuronal differentiation and circuit formation. DA receptors have characteristic laminar distribution in the cortex, as observed in the monkey, [^{3}H]SCH23390-labeled D_1 receptors have a bilaminar distribution with the highest concentration in the supragranular layers of the cortex (I,II and IIIa) and deep layers V and VI with relatively few receptors in intermediate strata. [^{3}H]raclopride-labeled D_2 receptors, on the other hand, are most concentrated in layer V and exist in lower densities than D_1 receptors throughout the cortex [Goldman-Rakic et al., 1990; Lidow et al., 1991]. Dense DA innervation into the superficial layers of cortex may be a primate specialization as binding in these layers has not been observed in rodents. The anatomical distribution of cortical DA receptors is heterogeneous throughout various brain regions, and corresponds with concentration of DA fiber input and endogenous DA and metabolites.

The majority of work thus presented has been done in the rodent, although comparisons have been made between species with available data on nonhuman primates and humans when possible and less often with rabbits. The characterization of the DA system in rabbits validates it as a relevant animal model for study (details further on). Pharmacological agents used to characterize D_1 receptors in the rat, nonhuman primate and humans have similarly been used in rabbits to characterize high-affinity receptors in the cortex and striatum with similar pharmacological profiles as described in the aforementioned species [Reader et al., 1989b]. Similarly, D_2 receptors have been characterized in the rabbit striatum and cortex [Dewar et al., 1989]. In the rabbit CNS, high levels of DA content are present within the anterior cingulate, while other cortical areas such as the somatosensory cortex and visual cortex have low levels of endogenous content. The highest concentrations of DA, as similarly observed in other species studied, are in the neostriatum with no differences between lateral and medial caudate or putamen in the rabbit. Receptor densities are heterogeneous between brain regions with the highest concentrations of D_1 and D_2 receptors in the striatum. In the striatum, D_2 receptors exist in a lateral to medial gradient in the caudate, findings consistent with observations in the rat. In the cortex, D_1 receptor density is significantly lower than in the striatum, but corresponds with areas of DA innervation. D_2 receptor density is also heterogenous, and less than D_1 receptor density in the cortex [Dewar et al., 1989; Dewar and Reader, 1989; Reader et al., 1989b].

In vitro studies have supported a role for DA as both a promoter and an inhibitor of neurite growth [Todd, 1992; Reinoso et al., 1996; Song et al., 2002; Stanwood and Levitt, 2007]. The actions of DA on outgrowth are modified by the complement of receptors that are activated, and as a function of the neuronal cell type being modulated. For example, in cortical neurons, selective D_1 receptor activation decreases neurite outgrowth in a dose-dependent manner, whereas D_2 receptor activation increases outgrowth. In striatal neurons, however, these effects are reversed, with D_1 receptor activation serving to promote neuronal differentiation and process outgrowth. DA signaling also appears to be involved in prenatal neurogenesis itself within the neuroepithelial precursors of the striatum and cerebral cortex, via influences on cell cycle length [Ohtani et al., 2003; Zhang et al., 2005]. The phenotypic differentiation and migration of inhibitory

GABAergic interneurons may also be modulated by dopaminergic stimulation [Crandall et al., 2007]. Studies from our laboratory and others investigating the effects of prenatal cocaine exposure suggest that modification of DA D_1 receptor signaling during a sensitive period of prenatal development induces permanent effects on circuit formation and function (see below). Recent data also suggests that transient overexpression of the D_2 receptor in the developing striatum can cause life-long changes in the activity of D_1 receptor systems in the prefrontal cortex [Kellendonk et al., 2006]. Finally, DA-dependent processes also alter postnatal development of brain circuits, especially during the periods of synaptic maturation and refinement.

Norepinephrine or Noradrenaline

Norepinephrine (NE) is synthesized and released by adrenergic axon terminals in both the CNS and the sympathetic division of the autonomic nervous system. In the CNS, the cell bodies of NE neurons are concentrated in the brainstem, particularly in the locus coeruleus of the dorsal pons where they are involved in diffuse projections to the neocortex [Segal et al., 1973; Levitt and Moore, 1978; Lindvall et al., 1978; Levitt et al., 1984]. NE is involved in mediating attention, anxiety, arousal, feeding behaviors, and learning and memory.

NE neurons are born at a relatively early time in the CNS of monkeys during the first quarter of gestation, approximately ED 30 for neurons in the medial locus coeruleus and ED 32/ED 33 for those situated more laterally. In rats, fluorescently labeled neurons are observed in the nucleus early in gestation, at approximately ED 13 [Olson and Seiger, 1972; Lauder and Bloom, 1974b]. The majority of NE axon terminals ascend to the forebrain in the dorsal tegmental bundle, dessucating almost immediately or more rostrally to join the ascending medial forebrain bundle. Fluorescence histochemistry suggests that developing axons enter the neocortex across multiple cortical layers; however, as the cortex matures, NE afferent input is most concentrated in a bilaminar pattern, predominantly in layers II and/or III (superficial) and V and/or VI (deep). There is heterogenerity in density of NE input between cortical regions with the somatosensory cortex receiving the densest NE innervation. NE fibers are also found intermingled with DA neurons in areas of the prefrontal cortex, as well anterior parts of the superior and inferior temporal gyri. NE innervation is sparsest in posterior parietal areas and occipital lobes including visual cortex [Levitt et al., 1984; Reader et al., 1989a]. These synapses mature during early postnatal life and the adult pattern of innervation is obtained by the end of the first postnatal week in rodents [Lauder and Bloom, 1975; Levitt and Moore, 1979]. In primates, there is a considerably longer maturation process postnatally as the first postnatal week in rodents is equivalent to the third trimester in primates.

NE synthesis requires DA as a precursor substrate. DA is trafficked by vesicular transport into adrenergic terminals where it is converted to NE by the enzymatic activity of DA β-hydroxylase [Segal et al., 1973]. Receptors sensitive to NE are divided into 2 classes, α- and β-adrenergic receptors, based upon the physiological response to catecholamines. The classes are further divided into subtypes, of which there exists α_1, α_2, β_1 and β_2 based on pharmacological profiles. In rodents, α_1- and α_2-adrenoreceptor expression can be detected 1 day after birth by specific radioligand binding. Receptor binding increases with age, reaching a peak between PD 18 and 21 before declining to reach adult levels after the fourth postnatal week [Morris et al., 1980]. A similar trend in ontogeny is apparent with β-adrenergic receptors, with these receptors not being detected before PD 7 [Harden et al., 1977; Pittman et al., 1980].

[^{3}H]clonidine labeled α_2-receptors in the monkey are predominately found in the superficial layers of the cortex, with a descending concentration gradient from layers I to VI. Similarly, the density of [^{3}H]prazosin-labeled α_1-receptors decreases from layers I to IV; however, there is a slight increase in receptor concentration in the deeper cortical layers. β_1 and β_2 receptors are most concentrated in the intermediate layers of the cortex [Goldman-Rakic et al., 1990]. Species differences exist between primates and rodents in stratification of receptor density. In the rat, the highest concentration of α_1-receptors are found in layers III and IV, and β receptors are homogenously distributed.

Both types of receptors alter the postsynaptic membrane potential by acting upon potassium and calcium channels. Like DA, NE is terminated by reuptake into the presynaptic terminal by a high-affinity transporter, where it is enzymatically degraded or inactivated by monoamine oxidase.

Serotonin (5-Hydroxytryptamine)

Serotonin (5-HT) is a well-known modulator of a variety of cognitive and behavioral functions, including sleep, sexual urge, anxiety, appetite, temperature regulation, learning and memory, and mood. As such, 5-HT imbalances are implicated in a variety of disorders such as depression, anxiety disorders and aggression [Olivier

et al., 1995; Lucki 1998; Gingrich and Hen, 2001]. 5-HT also exerts influence during specific critical periods during early development. Accumulated evidence indicates that 5-HT plays a role in many developmental processes, including neurogenesis; neuronal migration and differentiation; synaptogenesis; and craniofacial, cardiac and limb development, prior to assuming is role as a neurotransmitter in the mature brain [Whitaker-Azmitia, 2001; Gaspar et al., 2003; Persico et al., 2006]. 5-HT also plays crucial roles in thalamocortical patterning [Lebrand et al., 1996; Rebsam et al., 2002; Bonnin et al., 2007].

Serotonergic neurons are among the earliest neurons to be generated during development of the brain. In the monkey, serotonergic neurogenesis in the brainstem raphe nuclei is evident by the end of the first month of gestation in 2 distinct phases. Neurons in rostral raphe nuclei are generated between ED 28 and 35 with a peak genesis around ED 30. Caudal raphe nuclei are generated somewhat later with peak neurogenesis between ED 38 and 40 [Levitt and Rakic, 1982]. In rodents, 5-HT neurons are evident in the midbrain by ED 12 [Lauder and Bloom, 1974a], and by the fifth week of gestation in humans [Olson and Seiger, 1972; Sundstrom et al., 1993; Lambe et al., 2000]. One day after their generation, serotonergic neurons in the raphe can synthesize and release 5-HT from their growing axonal processes [Lidov and Molliver, 1982; Lambe et al., 2000]. Serotonergic terminals are found broadly throughout the forebrain, including the thalamus and cortex. In the cortex, serotonergic input is greatest in visual and somatosensory cortical areas, and less in prefrontal and temporal cortical regions. 5-HT levels increase prenatally through the early postnatal years before declining to reach adult levels [Whitaker-Azmitia, 2001].

Numerous 5-HT receptors exist and are grouped into 7 different families based on molecular cloning. Additional receptor motifs are created through the acts of mRNA splicing and editing events. Each receptor subtype possesses distinct cellular and/or regional distributions, pharmacological profiles and signal transduction systems. Most 5-HT receptors are heterotrimeric G protein-coupled receptors that activate calcium and potassium channels through intracellular signaling cascades. 5-HT_4, 5-HT_6 and 5-HT_7 receptors couple to the stimulatory $G_s\alpha$ protein to increase activity of adenylate cyclase. 5-HT_3 receptors, however, are ligand-gated ion channels [Hartig 1994; Jackson and Yakel, 1995].

5-HT receptors are also expressed early in prenatal development [Hellendall et al., 1993; Bonnin et al., 2006]. For example, 5-HT_2 receptor immunoreactivity is initially apparent in the cortex between ED 19 and PD 0 in rodents. After birth, there is a rapid increase in expression levels in layers II–VI followed by gradual decline to adult levels beginning around the second postnatal week [Morilak and Ciaranello, 1993]. In the adult, 5-HT_2 receptors are concentrated in the intermediate strata III and IV of the cortex. Receptor localization is consistent between rodents, monkey and humans [Goldman-Rakic et al., 1990; Morilak and Ciaranello, 1993]. Similarly, the same developmental trend is observed for expression of 5-HT_1 receptors. At birth, the percentage of receptors expressed varies among brain regions with densities ranging from 5 to 50% of adult levels. There is then a transient increase in expression levels followed by a decrease to adult levels during the first postnatal month [Pranzatelli, 1993]. In the adult monkey, 5-HT_1 receptors are found in highest concentrations in the superficial layers of the cortex [Goldman-Rakic et al., 1990]. 5-HT_1 receptor localization is consistent between monkey and human, while in the rat receptor density is greatest in layer V [Hoyer et al., 1986].

The synaptic effects of 5-HT are terminated by reuptake of the neurotransmitter into the presynaptic nerve terminals through a high-affinity 5-HT transporter (SERT). After reuptake, 5-HT is subsequently degraded by the enzymatic catabolic activity of monoamine oxidase. A number of neurotherapeutic drugs used in the treatment of depression and anxiety disorders act by inhibiting reuptake of the transmitter by SERT [Blakely et al., 1994; Jayanthi and Ramamoorthy, 2005; White et al., 2005].

Developmental Cocaine Exposure Alters Neurobehavioral Development

The primary pharmacological sites of action of cocaine and other psychostimulants in the brain are the high-affinity transporters for DA, 5-HT and NE. Cocaine binds to these transporter proteins and blocks the reuptake of the neurotransmitters; thus, prolonging their time in the extracellular space. This permits the monoamine to bind to its receptor proteins for more sustained periods, resulting in excessive activation of these receptors, particularly those located extrasynaptically. Cocaine, a drug of abuse in adolescents and adults, produces a host of neuroadaptations in the brain of the user which are associated with addiction [Hyman and Malenka, 2001], and can potently modulate monoaminergic

systems during prenatal development if the drug is used during pregnancy [Malanga and Kosofsky, 2003; Stanwood and Levitt, 2004].

Clinical reports on the impact of prenatal cocaine exposure have been diverse, as some suggest gross physical malformations, others observe specific deficits in cognitive and emotional development, and yet others indicate no detectable effects. The variable outcomes are at least in part the result of important covariates such as the timing and amount of cocaine use during pregnancy, polydrug use, and the quality of pre- and postnatal care [Karmel and Gardner, 1996; Richardson et al., 1996; Gingras and O'Donnell, 1998; Dow-Edwards et al., 1999; Mayes et al., 2003; Singer et al., 2004]. In particular, prenatal cocaine exposure can have long-lasting negative effects on cognitive and attention systems. For example, prenatal cocaine exposure predicts poorer perceptual reasoning IQ compared to nonexposed counterparts [Singer et al., 2008], impairments in procedural learning [Mayes et al., 2007], increased behavioral problems in school [Bada et al., 2007] and increased risk of oppositional defiant disorder and attention-deficit hyperactivity disorder [Linares et al., 2006].

Different animal models, designed to mimic human drug use during gestation, confirm that prenatal cocaine exposure results in specific and long-lasting behavioral, cellular and molecular changes [Mayes, 2002; Lidow, 2003; Harvey, 2004; Stanwood and Levitt, 2004]. However, the extent and nature of the cellular alterations vary across model systems. Deficits range from alterations in basic processes of neocortical development that result in altered cell production, migration and genetic regulation [Gressens et al., 1992; Lidow, 1995b; Lidow and Song, 2001; Crandall et al., 2004; Ren et al., 2004; Guerriero et al., 2005; Lee et al., 2008; Novikova et al., 2008], to more subtle changes in cellular morphology and molecular signaling cascades within DA-rich regions of the cerebral cortex [Jones et al., 1996; Jones et al., 2000; Stanwood et al., 2001a; Stanwood and Levitt, 2003; Stanwood and Levitt, 2007]. In contrast to the cellular effects, consistent behavioral changes including deficits in attention tasks, emotional reactivity, and the reinforcing properties of drugs of abuse that correspond with the human clinical literature are observed in a variety of animal models of prenatal cocaine exposure [Morrow et al., 2002; Rocha et al., 2002; Gabriel et al., 2003; Stanwood and Levitt, 2003; Thompson et al., 2005b; Malanga et al., 2008].

One unique animal model of prenatal cocaine exposure, to study the mechanisms underlying the complex long-term adaptive changes and the functional outcomes of in utero cocaine exposure, utilizes a low-dose regimen of intravenous prenatal cocaine exposure in the rabbit, which was initially selected for ease of intravenous administration. Furthermore, the pharmacokinetic profile of intravenous cocaine in the rabbit [Parlaman et al., 2007] closely models what is seen when human users abuse cocaine [Evans et al., 1996; Jenkins et al., 2002]. A number of studies have established that the prenatal dosing is not generally teratogenic, nor does it impact basic developmental parameters such as kit mortality, litter size, sex or growth rates [Wang et al., 1995b; Jones et al., 1996; Wang et al., 1996; Murphy et al., 1997]. However, through control of length of drug exposure, age at drug exposure, and dosing, we have delineated a critical window of time (ED 16–25) during which exposure to cocaine affects behavior, morphology and cellular composition [Stanwood et al., 2001a; Stanwood et al., 2001b; Stanwood and Levitt, 2003; Thompson et al., 2005b]. This window of time corresponds to the emergence of pre- and postsynaptic components of the DA system in the cerebral cortex [Stanwood et al., 2001a].

Neuroanatomical and molecular analyses in this model have delineated a number of highly specific changes in DA-rich cortical areas, including changes in GABA content, calcium binding protein expression and morphological changes in pyramidal cells [Murphy et al., 1997; Jones et al., 2000; Stanwood and Levitt, 2001; Stanwood et al., 2001b; Stanwood et al., 2006; Stanwood and Levitt, 2007]. The specific neuronal morphology alterations include a 40–50% increase in pyramidal neuron apical dendrite length within DA-rich cortical areas [Jones et al., 2000], which are involved in cognition and executive functioning tasks, including attention [Goldman-Rakic, 1996; Collette and Van der Linden, 2002; Elliott, 2003; Elston, 2003; Clark et al., 2004].

Consistent with the regional selectivity in the anatomical findings, extensive behavioral characterization of rabbits following in utero exposure to cocaine suggest that the behaviors disrupted appear to be limited to those mediated via select DA-rich cortical and subcortical regions [Romano and Harvey, 1996; Simansky et al., 1998; Gabriel et al., 2003; Stanwood and Levitt, 2003; Thompson et al., 2005b]. For example, these animals exhibit decreases in spontaneous alternation as measured by the Y-maze following prenatal cocaine exposure [Thompson et al., 2005b]. This decrease in attention is not accompanied by changes in open-field behavior or 2-object recognition. Additionally, offspring exposed to prenatal cocaine show a decreased number of head bobs, a measure of stereotypy, following a single injection of amphet-

amine, and display a blunted preference for cocaine in a conditioned place preference paradigm [Stanwood and Levitt, 2003; Thompson et al., 2005a].

Molecular analyses have determined that the DA D_1 receptor exhibits permanently reduced coupling to its cognate G protein, $G_s\alpha$, following prenatal cocaine exposure [Wang et al., 1995a; Friedman et al., 1996; Jones et al., 2000]. This reduction in coupling is a result of DA D_1 receptor remaining internalized and not trafficking properly to the cell membrane where it would then interact with $G_s\alpha$ [Stanwood and Levitt, 2007]. Adult rabbits exposed to cocaine prenatally also exhibit greatly reduced psychostimulant-induced stereotypies, consistent with diminished D_1 receptor signaling [Simansky and Kachelries, 1996; Stanwood and Levitt, 2003]. It is important to emphasize that other $G_s\alpha$-coupled receptor signaling is not altered, nor is D_2 coupling altered in the DA-rich brain regions [Wang et al., 1995a; Friedman et al., 1996]. This selective reduced coupling of the D_1 receptor has been implicated in the cellular, morphological and behavioral changes observed following prenatal cocaine exposure in our model. Additional evidence to support a role for altered D_1 receptor signaling at the cellular level comes from our recent study of the D_1 receptor knockout mouse, which exhibits similar cellular and morphological changes to the prenatal cocaine exposed rabbits [Stanwood et al., 2005].

Effects of Developmental Amphetamine/ Methamphetamine Exposure

Although amphetamine and methamphetamine use and abuse has been present for decades, there has been comparatively (to cocaine) little clinical and basic research on its effects on brain development. Reports have only recently emerged from a large prospective study [Smith et al., 2006; Smith et al., 2008]. Early clinical reports emphasized increases in premature delivery, placental abruption, cardiac defects and fetal distress [for reviews, see Plessinger, 1998; Smith et al., 2006]. In utero methamphetamine-exposed children are at high risk of growth impairment [Smith et al., 2003] and are 3.5-fold more likely to be smaller than average for gestational age [Smith et al., 2006], perhaps not surprising given the anorectic effects of the drug.

Even fewer studies have examined neurobehavioral outcomes specifically. In neonates, methamphetamine exposure is associated with lower arousal, more lethargy and increased physiological stress [Smith et al., 2008]. In a small retrospective study, significant deficits in visuomotor integration, attention and memory have been observed and linked to smaller volumes of the putamen, globus pallidus and hippocampus [Chang et al., 2004]. Imaging studies also point to alterations in striatal energy metabolism in children exposed gestationally [Smith et al., 2001; Chang et al., 2007]. It will clearly be important to continue to follow these children for impairments of this nature as they develop and enter schools.

Animal models utilizing a wide variety of species, doses and timing of exposure have been used to investigate the consequences of prenatal exposure on development. At high doses, methamphetamine induces prominent teratogenic effects on the neonate [Nora et al., 1965; Kasirsky, 1971]. A very good animal model of third trimester exposure has been developed by Vorhees et al. [2000, 2007], who inject neonatal rat pups during the ages spanning PD 11–21 with multiple spaced injections. This exposure paradigm produces selective effects on spatial learning and memory [Vorhees et al., 2000; Williams et al., 2003; Vorhees et al., 2007], and both transient and permanent effects in stress hormones and brain biogenic amines [Williams et al., 2005; Schaefer et al., 2008]. Interestingly, neonatal methamphetamine exposure does not alter striatal DA levels [Schaefer et al., 2008], very unlike its effect in adult animals, where it produces long lasting decreases in DA [Cappon et al., 2000].

Other groups have reported changes in the structure and myelination of the optic nerve [Melo et al., 2006, 2008], altered seizure susceptibility [Slamberova et al., 2008] and reduced spontaneous motor activity [Cho et al., 1991; Weissman and Caldecott-Hazard, 1993] following prenatal methamphetamine exposure. Long-lasting changes in the function of the NE [Nasif et al., 1999] and 5-HT [Tavares et al., 1996] systems have also been described following in utero amphetamine exposure.

Effects of Developmental MDMA Exposure

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a derivative of methamphetamine acting primarily on the 5-HT system to increase 5-HT release. In adults, MDMA produces enhanced mood, euphoria, heightened sensory awareness and sympathetic arousal, including tachycardia and hyperthermia [Lyles and Cadet, 2003]. At high doses, MDMA is capable of neurotoxicity. MDMA also passes through the placental barrier to enter into the fetal circulation [Campbell et al., 2006], suggesting that MDMA use during pregnancy is capable of inducing ef-

fects in the offspring. 5-HT has well-documented effects on early development of the brain and other organs [Cases et al., 1996; Bonnin et al., 2007; Cote et al., 2007], raising concerns about deleterious effects of MDMA use during pregnancy.

In fact, a preliminary study of prenatal MDMA-exposed children demonstrated increased risks of cardiovascular and musculoskeletal abnormalities following exposure during the first trimester [McElhatton et al., 1999]. Prenatal exposure in animal models and culture systems also suggest deleterious effects of MDMA on the development of dopaminergic and serotonergic neurons [Won et al., 2002; Koprich et al., 2003; Galineau et al., 2005] and increases in locomotor activity in adolescent offspring [Koprich et al., 2003]. Third trimester equivalent exposure in rats also leads to learning difficulties [Broening et al., 2001; Williams et al., 2003]; similar to the effects of the 5-HT releaser D-fenfluramine [Morford et al., 2002]. These effects may be due to increased sensitivity of 5-HT_{1A} receptors [Crawford et al., 2006], and were recently reviewed in exquisite detail [Piper, 2007; Skelton et al., 2008].

Potential Developmental Impact of Therapeutic Medications

Biogenic amine systems are also targeted by psychoactive medications, including antidepressant and antipsychotic drugs. To test for a possible developmental role of the 5-HT system in establishing anxiety circuitry, Hen and colleagues generated a conditional knockout mouse that allowed for temporally restricted rescue of postsynaptic 5-HT_{1A} receptors in the cerebral cortex and hippocampus [Gross et al., 2002]. Using this strategy, they demonstrated that initiating expression of the receptor after PD 21 resulted in increased anxiety levels identical to constitutive 5-HT_{1A} receptor knockout animals. Conversely, earlier expression of the 5-HT_{1A} receptor, during the first 3 postnatal weeks, produced mice with anxiety levels that were indistinguishable from wild-type animals, even if the receptor was turned off in adulthood. Administration of the selective 5-HT reuptake inhibitor fluoxetine from PD 4 to 21 also leads to permanent changes in anxiety behavior [Ansorge et al., 2004]. These findings indicate that normal 5-HT activity during early postnatal development in the rodent is crucial to the establishment of normal anxiety-modulating circuits in the brain, and that both genetic and environmental factors are capable of influencing these circuits.

Consistent with the rodent models, data from human studies suggest that baseline anxiety levels are influenced early in life. By 2 years of age, most children have established cohesive patterns of response to novel environments, as measured by behavioral inhibition. These measures appear to be stable over many years [Hirshfeld et al., 1992; Rosenbaum et al., 1993; Schwartz et al., 1999; see also Degnan and Fox, 2007], and can predict one's future risk of anxiety disorders [Kagan and Snidman, 1999; Kagan et al., 2007]. Not surprisingly, polymorphisms in 5-HT system-related genes have all been associated with anxiety- and depression-related symptoms [Albert and Lemonde, 2004; Kim et al., 2006; Walderhaug et al., 2007; Dannlowski et al., 2008; Murphy and Lesch, 2008]. Many prominent psychotherapeutics target the 5-HT system, and are utilized for depression and anxiety among pregnant and nursing mothers. Published literature to date suggests only modest alterations in neonatal outcome [Pearson et al., 2007; Andrade et al., 2008; Maschi et al., 2008; Oberlander et al., 2008], but further study of the neurobehavioral consequences of antidepressant exposure on the developing fetus and infant are clearly needed. Possible long-lasting changes in drug-seeking behavior following maternal 5-HT reuptake inhibitor exposure have also been recently suggested [Forcelli and Heinrichs, 2008].

Antipsychotic drugs are another group of therapeutics needed by some pregnant women and young people suffering from schizophrenia and other psychotic illnesses. Again, however, these drugs have potent effects on the development of aminergic systems, especially on DA receptors [Rosengarten and Friedhoff, 1979; Moran-Gates et al., 2006]. These drugs can also produce long-lasting changes in neurochemistry, brain architecture, and behavior [Scalzo and Spear, 1985; Scalzo et al., 1993; Singh and Singh, 2001; Rosengarten and Quartermain, 2002; Singh and Singh, 2002; Wang et al., 2006].

Another intriguing and unexpected example has come from developmental studies of terbutaline, a β-adrenoceptor agonist used to arrest preterm labor. However, the drug also crosses the placenta and blood-brain barrier. Early postnatal exposure to terbutaline in rats, a period corresponding to the third trimester in humans, produces long-lasting alterations in NE innervation and receptor expression in multiple brain regions [Slotkin et al., 1990; Slotkin et al., 2001; Rhodes et al., 2004; Aldridge et al., 2005; Slotkin and Seidler, 2007a], as well as increasing the toxic consequences of subsequent pesticide exposure (see 'Environmental Agents/Toxins') [Meyer et al., 2005]. Increased microglial activation, behavioral abnormali-

ties and alterations in 5-HT systems have also been reported [Aldridge et al., 2005; Zerrate et al., 2007]. In humans, it has been suggested that terbutaline treatment during pregnancy may lead to an increased incidence of autism spectrum disorder in offspring [Connors et al., 2005]; similarly gain-of-function polymorphisms in the β_2-adrenergic receptor which produce receptors that are resilient to desensitization have been associated with autism [Connors et al., 2005; Cheslack-Postava et al., 2007].

Environmental Agents/Toxins

Thousands of new chemicals are produced each year, about 25% of them may be neurotoxic, but only about 10% of them will ever be tested for such activity [Connors et al., 2008]. Long-lasting neurodevelopmental effects on biogenic amine systems and their targets have been described for some of these chemicals and environmental contaminants, including lead [Szczerbak et al., 2007; Nowak et al., 2008], polychlorinated biphenyls [Bushnell et al., 2002; Kuchiiwa et al., 2002], polybrominated diphenyl ethers [Dingemans et al., 2007; Llansola et al., 2007; Alm et al., 2008; Gee and Moser, 2008], pyrethroids [Nasuti et al., 2007], organic solvents [Hougaard et al., 1999; Gospe and Zhou, 2000; Bowen and Hannigan, 2006], and synthetic estrogens such as bisphenol-A [Suzuki et al., 2003; Laviola et al., 2005; Miyagawa et al., 2007]. These 'nondrug' environmental factors can interact with developmental drug exposures and/or genetic factors to produce complex effects on brain formation and function, often at concentration levels that appear to be harmless for adults. For example, perinatal exposure to bisphenol-A can produce long-lasting potentiation of D_1 DA receptor function, supersensitivity to methamphetamine and decreases in the expression of genes crucial for DA neuron development and survival, such as sonic hedgehog and glial-derived neurotrophic factor [Suzuki et al., 2003; Suzuki et al., 2005; Miyagawa et al., 2007]. Even artificial food colors and preservatives such as sodium benzoate appear to contribute to hyperactivity in children [McCann et al., 2007]. It is well beyond the scope of this review to describe all of these compounds in detail [for more detailed reviews, see Costa et al., 2004; Rodier, 2004; Slotkin, 2004; Bowen and Hannigan, 2006; Johansson et al., 2007; Moser, 2007], but we will very briefly discuss 2 classes of compounds with likely effects on the development of brain biogenic amines and their targets.

Organophosphate pesticides inhibit cholinesterases, and produce cholinergic overstimulation. In addition, developmental exposure to the compounds, such as chlorpyrifos, produces effects on serotonergic synaptic function [Slotkin and Seidler, 2007b; Moreno et al., 2008; Roegge et al., 2008]. Most exposure occurs through dietary intake [Lu et al., 2008]. Importantly, many of these effects on 5-HT and 5-HT-mediated behaviors, such as the development of emotional systems, occur at doses below the threshold for cholinesterase inhibition [Levin et al., 2002; Slotkin et al., 2006; Roegge et al., 2008]. Pre- and perinatal exposure also produces long-lasting changes in components of brain DA systems, and even increases cell loss at later developmental times following exposure to dopaminergic neurotoxins used to model Parkinson's disease [Richardson et al., 2006]. Recent studies identifying functional polymorphisms affecting chlorpyrifos metabolism [Berkowitz et al., 2004] and documenting decreases in cognitive development in children exposed to chlorpyrifos during gestation suggests that this is a very significant human health problem [Rauh et al., 2006; Engel et al., 2007].

Lastly, we describe data regarding manganese, a common naturally occurring heavy metal and essential nutrient. Manganese is crucial for maintaining the proper function and regulation of many biological processes, but is also used in numerous industries including welding, mining and formulating gasoline additives. Manganese is readily transported into the brain, either as a free ion species or as a nonspecific protein-bound species [Aschner and Gannon, 1994]. Chronic manganese overexposure results in the onset of a very specific neurological phenotype, known as manganism, which presents with motor symptoms resembling those of Parkinson's disease [Lee, 2000; Normandin et al., 2002; Guilarte et al., 2006; Aschner et al., 2007]. Similar symptoms have also been described in adults and children receiving prolonged total parenteral nutrition [Kafritsa et al., 1998; Nagatomo et al., 1999; Hsieh et al., 2007], which contains high amounts of manganese [Erikson et al., 2007].

Emerging data from both animal and human studies suggest a potent effect of developmental manganese exposure on brain development [Erikson et al., 2007; Ljung and Vahter, 2007]. For example, manganese exposure during pregnancy and/or early postnatal life produces alterations in locomotor activity, brain monoamine levels, oxidative stress and brain morphology [Pappas et al., 1997; Tran et al., 2002; Erikson et al., 2006; Reichel et al., 2006]. In children, preliminary studies have associated elevated manganese content in drinking water with de-

creased cognitive and attentional functions [Wasserman et al., 2006; Bouchard et al., 2007]. Increased prenatal manganese exposure has also been linked to childhood behavioral disinhibition [Ericson et al., 2007]. Moreover, iron deficiency can enhance brain manganese accumulation, even in the absence of excess manganese in the environment, and produce long-lasting changes in metal concentrations and transporters in the brain [Garcia et al., 2007]. These data warrant a reassessment of guideline values for acceptable manganese levels and much more detailed investigations into the risks of environmental manganese exposure.

Conclusions

The mammalian brain develops over a protracted period of time. Neurodevelopment is affected by both genetic and environmental influences, within the context of evolving time. Environmental influences can have effects on brain architecture both prenatally, within the mother's womb, and by the physical and chemical environment experienced after birth. Compounds which affect the construction of brain circuits include legal and illicit psychoactive drugs, used either medicinally or recreationally, as well as environmental toxicants and natural contaminants. Biogenic amine systems may be particularly sensitive to such modulation. Resulting disruptions in brain development sometimes do not emerge until later in life, and may be produced at dose levels that are relatively harmless for adults. This makes the study of these long-term impacts very challenging, but also very crucial. Scientists must continue to inform the public and policy makers of these complex and important issues.

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