Altering the course of neurodevelopment: a framework for understanding the enduring effects of psychotropic drugs

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Received 16 April 2004; received in revised form 7 June 2004; accepted 7 June 2004

Abstract

Childhood is a time filled with wondrous changes, as brain plasticity permits experiences to shape the immature brain to meet the demands of the environment. Change occurs at various levels—from neuroanatomy, including within a given region and its connectivity to other regions, to the function of neurotransmitter systems and their reactivity to pharmacological agents in the short- and long-term. The nature and degree to which drug exposure influences the final adult topography is influenced greatly by the maturational phase of these critical factors. Moreover, evidence is slowly emerging that suggests that the long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation (i.e., typically during adulthood). This phenomenon is known as neuronal imprinting and occurs when the effects of drug exposure outlast the drug itself. Thus, understanding the persistent effects critically depends on the window of observation. Embracing this concept should influence how we conduct preclinical assessments of developmental drug exposure, and ultimately how we conduct clinical assessments of drug efficacy, effectiveness, and safety for the treatment of childhood psychiatric disorders. In this article, we present a model to provide a heuristic framework for making predictions about imprinted effects of childhood drug exposure. We then review epidemiological data on attention deficit hyperactivity disorder (ADHD) and childhood depression, prescription practices, and what is known regarding the long-term consequences of drug exposure in these populations. We conclude with a discussion of the current status of preclinical studies on juvenile stimulant exposure.

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Keywords: Adolescence; Antidepressant; Child; Fluoxetine; Imprinting; Methylphenidate; Postnatal

1. Developmental framework

1.1. Introduction

Preclinical research efforts to elucidate the enduring effects of drugs have focused primarily on prenatal exposure to these agents, often at doses aimed at determining the toxicological effects they exert on brain development (McGivern and Handa, 1996; Levitt et al., 1997; Lidow, 1998; Malanga and Kosofsky, 1999; Ernst et al., 2001). An impressive level of resiliency is observed in these animals (and these studies are reviewed elsewhere in this volume), especially when compared with equivalent exposure during adulthood. However, while prenatally-exposed animals do not appear to be affected immediately by treatment, examination of these animals later in life paints a different picture (Kosofsky and Hyman, 2001; Andersen et al., 2002a,b). Simply put, drug effects incubate. Decades of neuroteratology research have shown us that the expression of these effects is delayed, making their presence known in adulthood (Andersen, 2003). This concept is known as neuronal imprinting, in which drug effects outlast the drug itself (Hess, 1972; Andersen, 2003). While we have learned a tremendous amount about prenatal drug exposure,
society faces the new emerging issue of understanding the enduring effects of early postnatal drug exposure—mainly in the form of prescription medication for children.

1.2. The scope of the problem: the clinical picture

When faced with the prospect of prescribing medications to children, clinicians are being challenged with increasingly complex and difficult decisions. The importance of the acute treatment of symptoms must be carefully weighed against the potential for unknown long-term side effects resulting from the medication (Schachar et al., 1997; Pliszka, 1998; Henry et al., 2003; Vaswani et al., 2003). Nonetheless, statistics show that children are initiated into stimulant and antidepressant pharmacotherapy at progressively younger ages (e.g., 2 years of age) and that pediatric pharmacotherapy in general is increasing in prevalence (Minde, 1998; Zito et al., 2000; Goodwin et al., 2001; Olfson et al., 2002). Surprisingly, despite the obvious need for such information, the long-term effects of therapeutic drug exposure on an immature brain have not been adequately assessed at either the clinical or preclinical stage. Taken together, the largest contribution of postnatal drug exposure arises from prescription medications. Table 1 provides an index of frequency of prescription rates occurring for various stimulants, including methylphenidate (MPH) and amphetamine, and antidepressants, including fluoxetine.

Why has the need for long-term studies of medication exposure in children received so little attention until recently? A number of possibilities exist, but a few key reasons predominate. First, treatment of childhood psychiatric disorders is difficult and not taken lightly by clinicians and family members (Ryan, 2003). However, as the need to treat acute symptoms outweighs any possible long-term enduring risks, therapy begins. Prevention of future depressive episodes (kindling) that often become progressively more severe is important (Costello et al., 2002). In addition, numerous long-term, positive benefits have been documented that are secondary to treatment. For example, children treated with stimulants for their attention deficit hyperactivity disorder (ADHD) exhibit improved social skills and academic progress (Hechtman et al., 1984; Greenfield et al., 1988, 1999; Greene et al., 1999) and reduced drug abuse liability (Biederman et al., 1999; Wilens et al., 1999). This latter observation is surprising because ADHD itself is a risk factor for substance abuse, conferring a two-fold greater risk in the adult ADHD population than the normal population (Gittelman et al., 1985; Biederman et al., 1995; Biederman et al., 1997; Milberger et al., 1997). Second, the acceptance that the plasticity of the developing brain is vastly different than that of the adult brain is slowly emerging (Spear, 2000; Slotkin et al., 2002). This recognition may be best evidenced by the recent provision by the US Food and Drug Administration (FDA) to grant an additional 6 months of patent protection if drug effectiveness studies are conducted with children and adolescents (Ryan, 2003). Third, the same initial mechanisms of therapeutic action for psychotropic medications are utilized in both the immature and mature brain. This observation has provided a false sense of safety by implying that the long-term effects in children must be comparable to those in adults. As discussed later, the maturational state of the underlying target system is critical for determining the long-term effects of drug exposure (Andersen et al., 2002a,b). For the major psychiatric disorders, therapeutic action occurs primarily in monoamine systems that mature between adolescence and young adulthood; therefore, exposure prior to this point affects systems that are still immature and potentially vulnerable. Fourth, the largest obstacle to elucidating the enduring effects of childhood psychotropic medication lies in the choice of targets to study. For example, chronic stimulant exposure in adults causes an increase in the addictive-like properties (Robinson et al., 1982; Peris and Zahniser, 1987; Kalivas et al., 1998; Vanderschuren et al., 1999) and research efforts on stimulants have concentrated primarily here. However, the reverse is observed following childhood exposure—both clinically (Hechtman and Weiss, 1986; Biederman et al., 1999; Wilens et al., 1999; Loney et al., 2002) and preclinically, in which rats exposed pre-pubertally demonstrate either a reduced sensitivity to dopamine agonists (Dow-Edwards and Busiden, 2001), or an aversion (Andersen et al., 2002a,b; Bolaños et al., 2003). Taken together, a new paradigm is needed to better predict more appropriate symptoms to study.

1.3. Drug prevalence and utilization in pediatric populations

Stimulants and antidepressants are the two main classes of psychotropic drugs prescribed to children and adolescents. Stimulants are legally prescribed to an estimated 4 million children taking the drug annually in the US alone (Zito et al., 2000; Connor, 2002). As adolescents are included, illegal stimulant use and abuse rises sharply between the ages of 12 and 16 years, increasing from 2.9% to 16.4%, respectively (SAMHSA, 1999). Exposure to antidepressants during childhood represents one of the fastest rising treatments in the psychiatric community (Zito and Safer, 2001; Zito et al., 2002). Prescription rates for fluoxetine rose 1.8-fold between 1991 and 1995 in elementary and preschool children in the United States (Zito et al., 2000), whereas a 10-fold increase in the use of selective serotonin reuptake inhibitors (SSRI’s) in children 5 years of age and younger was observed between 1993 and 1997 in Canada (Minde, 1998). Preschoolers (0–5 years) continue to represent the fastest rising group, as recent statistics from the United States suggest that antidepressant use has doubled in girls and increased 64% in boys between 1998 and 2002 (Delate et al., 2004).

Unlike the known potential risk of addiction that is associated with stimulant prescriptions in adulthood (Chambers and White, 1980; Brown and Chaitkin, 1981), the untoward profile associated with antidepressants has not
been adequately addressed. Exposure to antidepressants in adulthood is not believed to have any long-term consequences (Greden, 1993; Mourilhe and Stokes, 1998; Antonuccio et al., 1999). Therefore, it is either presumed that the same applies to juvenile populations or the enduring effects are unknown. More importantly, the course of illness is typically poor if antidepressants are needed at younger ages, thereby necessitating some form of treatment despite the unknown long-term risks (Ryan, 2003). However, recent controversial findings (discussed in detail in Section 3.2) implicate the use of SSRI’s in childhood as a risk factor for subsequent suicidal behavior. Conversely, little research is available on the outcome of unmedicated childhood depression due to inherent risks of developing other psychiatric

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a MEPS = Medical Expenditure Panel Survey; NAMCS = National Ambulatory Medical Care Survey.
b SSRI = Selective Serotonin Reuptake Inhibitor; MPH = Methylphenidate; TCA = tricyclic antidepressant.
disorders, abusing substances, committing suicide, and having poor academic, work, and social functioning (Emslie et al., 2003). The increased prevalence of suicide from 1.6/100,000 in children 10–14 years old to 9.7 per 100,000 in adolescents (15–19 years old) underscores the importance of effective treatment (Guyer et al., 1998).

1.4. Theoretical framework of enduring drug action

The central tenet of this article is that drug exposure during childhood and adolescence alters the development of brain regions where the drugs are active. As a result, the normal developmental trajectory of any given underlying circuitry is changed in such a way that differs from what would be predicted based on exposure during adulthood (Andersen, 2003). Drugs such as neuroleptics (Rosengarten and Friedhoff, 1979) and stimulants (Andersen et al., 2002a,b; Bolanos et al., 2003) have delayed effects on anatomy and function that are not apparent until adolescence or later. While we understand little about the adaptive processes underlying these changes, the effects are more extensive and permanent when compared with adult exposure to the same drug (Andersen, 2003). The hypothesis of “equal, but opposite” (Andersen, 2003) captures how these effects manifest themselves (Fig. 1). Specifically, chronic drug exposure in adult animals results in an accommodation to the effects that occur by a series of compensatory reactions (Creese et al., 1977; Nestler and Aghajanian, 1997; Brunello et al., 2002; Cryan et al., 2002). In contrast, chronic drug effects are assimilated in juvenile animals by incorporating drug-induced changes in the form of permanent developmental alterations of the system (Norrholm and Ouimet, 2000; Lidow and Song, 2001; Andersen, 2003). We will review relevant theories of environmental interactions with developing neurobiology, the “equal, but opposite” hypothesis, and clinical and preclinical literature demonstrating neuronal imprinting. Taken together, chronic, early childhood exposure to stimulants and antidepressants may actually exacerbate symptoms later in life in some cases, rather than reduce them, or even result in a new constellation of psychiatric symptoms.

1.5. Overproduction and pruning of synapses during development

The period of adolescence is integral for the long-term nature of imprinted drug effects and may be the critical period that differentiates this early imprinting versus the more compensatory reaction to chronic drug exposure observed in adulthood. Numerous anatomical and pharmacological transitions serve as a neural guide or stabilization mechanism during adolescence (Insel, 1995) that resolve in the predominant adult “state”. For example, monoamine systems in the mammalian species exuberantly overproduce then reduce synapses and receptors in humans (Huttenlocher, 1979; Giedd et al., 1999a,b; Thompson et al., 2000; Sowell et al., 2001), primates (Lidow et al., 1991), and rats (Andersen et al., 1997a,b; Andersen et al., 2000).

![Fig. 1. Diagram illustrating the different trajectories of drug response that depend on maturational stage of exposure. Top: adult (post-pubertal) drug exposure (left) produces an improvement in symptoms that increases with time. Upon withdrawal (right), response to drug challenge returns to original baseline levels. Bottom: Juvenile (pre-pubertal) drug exposure (left) may (or may not) also produce symptom improvement or sensitized response. Once the drug is withdrawn, response to drug challenge wanes with time in a manner similar to adults, but then continues to transform after puberty and manifests as the opposite of the original target of pharmacotherapy. This transformation may include the appearance of adaptive (e.g., tolerance to stimulant effects; (Andersen et al., 2002)) or maladaptive characteristics (e.g., anhedonia following pre-pubertal stimulant exposure; (Bolanos et al., 2003; Carlezon et al., 2003)), or possibly depression in response to antidepressants (Mirmiran et al., 1985).](image-url)
The reduction process is referred to as pruning, and as many as 40% of the synapses are lost during adolescence. The observations that overproduction and pruning occur in a regional (Huttenlocher, 1979; Andersen et al., 2000) and sex-related manner (Andersen et al., 1997a,b; Giedd et al., 1999a,b) may result in selective vulnerabilities for different brain regions, such that drug exposure will have its greatest impact on areas undergoing more active development than those that have reached their adult status (Lidow et al., 2001; Andersen, 2003). With increasing use of magnetic resonance imaging (MRI), we will be able to better document changes in normal development, disease course, and medication effects. Researchers at the US National Institute of Mental Health (NIMH) have already demonstrated the overproduction and pruning of gray matter in the cortex with males reaching a peak at 12.4 years and girls at 11.6 years (Giedd et al., 1999a,b), and have shown that excessive pruning of gray matter occurs in individuals with child-onset schizophrenia (Rapoport et al., 1999).

A number of functional transitions occur as well. For example, the 5-HT7 receptor is transiently expressed during postnatal development (Vizuete et al., 1997). We have shown that cortical dopamine activity is transiently modulated by an autoreceptor-like process that is lost with the onset of adolescence (Teicher et al., 1991; Andersen et al., 1997a; Teicher et al., 1998). The loss of this regulation occurs simultaneously with the emergence of adult-typical function of this area (Lyss et al., 1999). Pharmacologic sensitivity also changes to stimulants (see Fig. 2); (Andersen and Gazzara, 1994; Andersen and Gazzara, 1996; Andersen et al., 2001). Surprisingly, the developmental profile to antidepressants has not been investigated.

1.6. Theories on developmental transitions and selective vulnerability

Two prevailing theories have been proposed to explain the nature of postnatal overproduction and pruning (LeDoux, 2002). The first, initially coined as “neural Darwinism” by Edelman (1993), posits that the brain “selects” synapses to retain into adulthood that allow it to match the needs of the environment by controlling the pruning process (Piatelli-Palmarini, 1989; Teicher, 2002). For example, exposure to repeated maternal separation, considered a form of species-relevant stress, prevents the overproduction of synapses during adolescence and further reduces synaptic density in adulthood (Andersen and Teicher, 2004); it is believed the same process underlies the “wiring” of the brain of an abused child (Teicher, 2002). Alternatively, the “instructionist” viewpoint suggests that the environment “instructs” the brain to develop in a certain manner based on use and need and constructs the brain (anatomically and/
or functionally) accordingly (Quartz and Sejnowski, 1997). For example, transplanted tissue from one region acquires the properties of the host. Both processes may actually be at play during maturation, but in a regional-dependent manner (LeDoux, 2002). For example, higher, cognitive structures such as the cortex may be influenced to a greater extent by environmental inputs, whereas lower, subcortical structures may be under greater control from genetic predisposition.

Environmental activation can program brain development, although the underlying genotype will have some influence. For example, the negative affect and stress that accompanies child abuse selectively affects the amygdala and hippocampus (Teicher, 2002). In this manner, the changes that are observed are specific for the system that is activated. Alternatively, the genotype biases the individual to seek environments that allow a given phenotype to be expressed (Tarter et al., 1999). Here, risk-taking and novelty-seeking (Wills et al., 1994; LaHoste, 1996; Comings and Blum, 2000) may lend themselves to promoting substance use disorder (SUD).

Independent of the nature–nurture debate, exposure to psychotropic agents during this developmental phase will act to either instruct the wiring of the brain or select existing synapses. One of the many possible mechanisms the brain will use includes alterations in monoamine levels. All three of the monoamines have been shown to have trophic roles. Dopamine (Kalsbeek et al., 1988; Lankford et al., 1988; Gelbard et al., 1990; Todd, 1992), norepinephrine (Feeney and Westerberg, 1990; Kline et al., 1994) and serotonin (Lauder and Krebs, 1978; Kuppermann and Kasamatsu, 1984; Whitaker-Azmitia and Azmitia, 1986) can increase synaptic sprouting, axonal growth, and synapse formation early in development. It is vitally important to note that, at least for serotonin, trophic effects are concentration-dependent (Mazer et al., 1997), suggesting that baseline levels are important for the nature of effect. Altering neurotransmitter levels will have its greatest impact during childhood to adolescence, when the synaptic selection process reaches its peak. Fig. 3 provides a comparative timeline between brain development and the timing of dopamine-related disorders.

Persuasive evidence exists that manipulations of the brain during critical periods may alter future, mature neuronal function by changing the developmental trajectory of any system. Administration of drugs that increase dopamine or norepinephrine neurotransmission, including MPH, early in life can effect change well after the drug is absent (i.e., imprinting) (Hess, 1972; Lerner et al., 1977). For example, stimulants produce sensitization in both young (Laviola et al., 1995; McDougall et al., 1999) and adult (Carr and White, 1983; Martin-Iverson et al., 1985; Koob and Weiss, 1992; Gaytan et al., 1997; Schenck and Partridge, 1999) animals. Following chronic exposure in adult animals, the response to the stimulant increases with time (Robinson et al., 1982; Peris and Zahniser, 1987; Vanderschuren et al., 1999). This adult-like sensitization occurs with the onset of adolescence in the rat (Brandon et al., 2001). In contrast, pre-adolescent exposure to stimulants results in sensitization that wanes within days since the last exposure (Laviola et al., 1995; McDougall et al., 1999; Collins and Izennwasser, 2002), and subjects already demonstrate reduced novelty-seeking (Kunko et al., 1996). Furthermore, reverse-sensitization, or tolerance, follows chronic pre-adolescent stimulant administration and occurs with the passage of time. These effects are even more dramatic when examined in adulthood. Postnatal exposure reduces locomotor sensitization to challenge with cocaine (Dow-Edwards and Busidan, 2001; Andersen et al., 2002a), amphetamine (Melnick and Dow-Edwards, 2001) and the direct agonist apomorphine (Busidan and Dow-Edwards, 1999) in adulthood. As the preclinical data and theories suggest, exposure to drugs (mainly stimulants in this example) results in different long-term effects depending on the age of exposure.

Specifically, the “equal, but opposite” hypothesis proposes that chronic drug exposure in adult animals results in an accommodation to the drug effects that occurs by a series of compensatory reactions. Conversely, chronic drug effects in juvenile animals leads to assimilation by incorporating drug-induced changes in the form of permanent developmental alterations of the system (Andersen, 2003). In the following section, data will be presented from clinical studies of children, adolescents, and young adults and preclinical studies that are consistent with this hypothesis.

2. Attention deficit hyperactivity disorder

2.1. The clinical disorder

ADHD is the most prevalent childhood psychiatric disorder that affects approximately 6% of school-aged children (Bird et al., 1988). As its namesake suggests, the core
symptoms of ADHD are motoric overactivity and inattention, but the full clinical presentation is much more heterogeneous and involves complex motor and cognitive processes (Barkley and Biederman, 1997; Teicher et al., 1997). Neuroanatomically, regions that subserve these functions are implicated in the pathophysiology of ADHD. Morphometric MRI studies report reductions in the corpus callosum, prefrontal cortex, caudate nucleus, and the globus pallidus in some (Castellanos et al., 1994; Casey et al., 1997; Faraone and Biederman, 1998; Lou et al., 1998), but not all studies (Rubia et al., 2000). The reductions tend to be lateralized to the right hemisphere (Casey et al., 1997). Normal age-related decreases in the size of the caudate are not seen in children with ADHD, which could reflect errors in the overproduction or elimination of synapses (Castellanos et al., 1994), and more recent reports suggest that children with ADHD overall have 3–4% smaller total cerebral volume (Castellanos et al., 2002). Hypofunctioning of the cortex has been proposed to explain reduced attention and impulsiveness (Dinn et al., 2001), and is improved by stimulant pharmacotherapy (Solanto, 1998). Hyperfunctioning of the striatum underlies increased motor activity (Teicher et al., 1997) and also benefits from drug treatment (Vaidya et al., 1998). The cerebellar vermis also plays a role in the pathophysiology of ADHD (Houk and Wise, 1995; Berquin et al., 1998; Anderson et al., 2002a,b; Castellanos et al., 2002).

2.2. Stimulant effectiveness in ADHD

Since the 1930’s, stimulant medications have been used to effectively ameliorate ADHD symptoms (Brady, 1937) and today are the first-line treatment of choice (Greenhill et al., 2002). In fact, stimulant use is on the rise in pediatric populations with 4 million children taking the drug annually in the US alone (Minde, 1998; Zito et al., 2000; Connor, 2002). The Multimodal Treatment Study of Children with ADHD (MTA; the most comprehensive study to date on the effectiveness of stimulant treatment involving 576 children with the diagnosis; (Anon., 1999) found that MPH was superior to behavioral treatment and routine community care that included medication. Although combined treatment (i.e., MPH + behavior therapy) provided some advantages for associated symptoms (e.g., deficient social skills, reading disability), MPH treatment alone had equivalent benefits compared to combined treatment for the core symptoms of hyperactivity and inattention.

The treatment of ADHD with stimulants seems counter-intuitive at first: children are hyperactive and have a higher risk of developing a SUD later on in life (Rounsaville et al., 1991). Upon closer examination, Rapoport and colleagues (Rapoport et al., 1978) found that acute stimulant administration improves performance in typical children as well, suggesting that the effects of MPH are not paradoxical, but rather exert rate-dependent effects on motor and cognitive activity (Rapoport et al., 1978; Teicher et al., 2003). Stimulants exert their euphorogenic effects in adults primarily via the dopamine system (Wise, 1996; Volkow et al., 1999a,b); however, stimulant use produces dysphoria in children, precluding its abuse liability (Rapoport et al., 1980). This dysphoria changes to euphoria with maturation in that stimulants become more enjoyable and their rewarding effects increase. The change from dysphoria to euphoria may represent the normal trajectory of the reward system, and may be altered as a consequence of stimulant exposure.

Quite remarkably, very little is known clinically about the enduring effects of childhood stimulant exposure. For example, we know that MPH use during childhood produces temporary decreases in weight gain that are not apparent by adulthood (Rapoport et al., 1978; Spencer et al., 1998), although reports of growth retardation following exposure in preschoolers are emerging (Swanson and Volkow, 2003). Curiously, 60% of children and adolescents with ADHD grow out of their symptoms and the disorder wanes by adulthood (Klein and Mannuzza, 1991). This different developmental trajectory for ADHD may possibly be the by-product of medication exposure.

Part of the reason that we know precious little about brain function is because assessment of functional brain activity in children with ADHD is difficult and limited for a number of technical reasons. Heterogeneity in the phenotype of ADHD may potentially mask subtypes with specific neurobiologies. Second, functional imaging with positron emission tomography (PET) imaging with radioactive ligands is difficult and controversial in children. Ernst and colleagues have documented elevated [18]-fluoroDOPA accumulation in the right midbrain that correlated with symptom severity (Ernst et al., 1999). Together, these issues have hampered our understanding of disease course and medication effects in pediatric populations.

New approaches to studying children are becoming more widespread. With the use of T2-relaxometry, which does not involve radioactivity, and continuous performance tasks, Teicher and colleagues demonstrated that attentional performance negatively correlates with T2-relaxation time in the caudate and cerebellar vermis of children with ADHD (Teicher et al., 2000; Anderson et al., 2002a,b). Vaidya et al. (1998) examined the effects of medication on functional activity with blood oxygen level dependent (BOLD) imaging and suggested that the mechanism of stimulant action differs between typical children and those with ADHD. These investigators also propose that MPH selectively activates the prefrontal cortex and reduces activity in the striatum of children with ADHD, but not in typical children (also see Kim et al., 2001). Although these results may point to the underlying pathophysiology, they also must be interpreted with caution as all of the children with ADHD had prior stimulant exposure of unknown duration and the dose between ADHD subjects and controls was not controlled.

Findings of alterations in brain structure as a function of medication exposure are beginning to emerge in the literature. First, Krause et al. (2000) showed a reduction in
dopamine transporter (DAT) after four weeks of MPH treatment in a previously unmedicated ADHD adult population. Second, data from Castellanos et al. (2002) in a large-scale study suggest that white matter is decreased in non-medicated children with ADHD relative to medicated children with ADHD (8.9% larger) and age-matched controls (10.7%). Less white matter suggests slower processing within and between regions. Medication had no significant effect on gray matter, although function was not assessed. No long-term, chronic exposure studies have been conducted on brain function to determine the effects of drug imprinting on the immature human brain.

2.3. Effects of juvenile exposure to stimulants

The majority of animal studies that have examined the effects of juvenile exposure to stimulants have done so to produce sensitization as a means of studying plasticity. The results following juvenile exposure are often opposite than those observed in adult-exposed animals, especially if examined well-after drug withdrawal. For example, increased extracellular levels of dopamine are often reported following adult stimulant exposure 11–15 days after treatment (Kaliwas and Duffy, 1988; Keller et al., 1992). In contrast, a 50% decrease in extracellular dopamine is observed following neonatal cocaine (25 mg/kg) 12 days post-treatment, and levels return to control values by 26 days at the onset of puberty (Howard et al., 1997). Furthermore, juvenile exposure may alter innervation patterns. Neonatal cocaine exposure is believed to change dopaminergic innervation (Howard et al., 1997; Diaz Heijtz et al., 2003). Juvenile exposure to amphetamine increases dendritic branching in the prefrontal cortex, but has no effect in the accumbens (Diaz Heijtz et al., 2003). Behavioral changes to dopaminergic challenges also support these findings and are discussed in Section 1.6 above. Changes within the genome are also occurring as indicated by increased c-fos immunoreactivity in the striatum following acute MPH exposure during early development (Penner et al., 2002), but attenuated expression after exposure in adults (Brandon and Steiner, 2003). Taken together, these data suggest that pre-pubertal exposure to stimulants reduces responsiveness to challenge during adulthood whereas post-pubertal exposure increases responsiveness.

Lately, efforts to more appropriately model childhood stimulant exposure are underway (Andersen et al., 2002b; Kuczenski and Segal, 2002) and are focused on much lower doses (2 mg/kg or lower) and route of administration (Kuczenski and Segal, 2002). Pre-clinically, two mg/kg or less produces plasma concentrations of MPH (8–40 ng/ml; Aoyama et al., 1990; Wargin et al., 1983). Clinically, a dose of 0.5 mg/kg produces plasma levels of approximately 10 ng/ml, which are considered optimal (Swanson and Volkow, 2003). Differences in pharmacokinetics produced by i.p. versus oral administration also need to be taken into consideration. Oral administration has a slower time course of action as well as lower overall peak drug levels (Ger asiminov et al., 2000; Swanson and Volkow, 2003). Moreover, oral administration is approximately half as effective (as indicated by locomotion and dopamine release) than i.p. administration (Ger asiminov et al., 2000). Intragastric metabolism of MPH hydrolyzes the l-MPH enantiomer with only the d-MPH having activity, thus accounting for lowered potency of oral administration.

Under these circumstances, exposure to low doses of the stimulant produces a long-lasting aversion to a moderate dose of cocaine (Andersen et al., 2002a) and other natural substances (Bolanos et al., 2003) and increases depressive-like symptoms (Carlezon et al., 2003) and anxiety (Bolanos et al., 2003). Moreover, Kuczenski and colleagues (Kuczenski and Segal, 2002) have now been able to demonstrate the sedating effects of MPH in rats by testing them with 0.75–3.0 mg/kg per os during their active cycle at night. As researchers become increasingly sensitive to the issues of age of exposure, dose, and dosing regimen, more clinical/preclinical parallels will be drawn. Better animal modeling of the enduring drug effects in a species with a shorter lifespan will enhance our knowledge much quicker than waiting decades to study the effects of childhood exposure.

3. Childhood depression

3.1. The clinical disorder

Depression during childhood has received recent increased attention from the medical community and the general public. Epidemiological studies show that major depression is comparatively rare among children (1–2%), but more common among youth, with up to a 25% lifetime prevalence by the end of adolescence (Essau and Dobson, 1999; Kessler et al., 2001). More conservative estimates of the disorder are between 1% and 3% in the teenage years (Roberts et al., 1995; Lewinsohn et al., 1998; van Dulmen et al., 2002), with the following symptoms as the primary clinical manifestations: feeling blue, depressed mood, feel too tired, feel life is not worth living, and poor appetite (van Dulmen et al., 2002). Childhood anxiety is also comorbid with depression (Kaufman and Charnley, 2000), and also responds well to antidepressant agents. Overall, the clinical presentation and course of depression are believed to be relatively the same across childhood, adolescence, and adulthood (Kovacs, 1996).

The brain regions that are affected by childhood/adolescent depression are comparable to those affected in adulthood. Childhood depression has been associated with smaller whole brain volume; however, most of the changes are restricted to frontal lobes. Reduced frontal white matter volumes (Steingard et al., 2002) with an increased prevalence and severity of white matter signal hyperintensities (Lyoo et al., 2002) and increased frontal gray matter
volumes are observed (Steingard et al., 2002). Emerging electrophysiological findings also implicate frontal lobe dysfunction (Steingard et al., 2000), and the effects in frontal cortex may be lateralized. Larger left-sided, but not right-sided, prefrontal cortical volumes are reported (Nolan et al., 2002) as well as reduced regional cerebral blood flow (rCBF) in the left anterofrontal lobe (Tutus et al., 1998). A decrement in P300 amplitude and increased alpha power, especially in the right frontal cortex, are present in older adolescent girls with a lifetime history of major depression (Bauer and Hesselbrock, 2002; Houston et al., 2003). Elevated choline levels in left, but not right, dorsolateral prefrontal cortex (Farchione et al., 2002) and orbitofrontal cortex (Steingard et al., 2000) are also observed. Changes are not only associated with frontal cortex as depressed adolescents have reduced rCBF in the left parietal lobe, right caudate, and anterior thalamus (Kowatch et al., 1999), which is consistent with adult findings.

Involvement of the amygdala in childhood depression has also been recently documented. Findings include larger left bilateral amygdala:hippocampal volume ratios (MacMillan et al., 2003); lower left amygdala choline:creatine-phospho-creatine ratios (Kusumakar et al., 2001); and blunted amygdalar response to fearful faces (Thomas et al., 2001). In a recent study, children and adolescents with depression had higher 5-HT transporter availability in the hypothalamic/midbrain region compared to children with other psychiatric disorders (Dahlstrom et al., 2000). However, these findings are difficult to interpret given that typical children were not included in the study.

Underlying hormonal changes associated with childhood depression may not follow the adult patterns. Whereas approximately 50% of adults demonstrate hypercortisolemia, the majority of children or adolescents do not demonstrate such increases in cortisol (Dahl et al., 1989; Puig-Antich et al., 1989; Birmaher et al., 1992) nor do they demonstrate blunted ACTH response to CRH infusion (Ryan et al., 1992; Birmaher et al., 1996; Dorn et al., 1997). Recently, Luby et al. (2003) showed that depressed preschoolers had increased cortisol levels in response to separation stressors, suggesting an age-appropriate stimulus may be needed. Furthermore, between 50% and 70% of children and adolescents are dexamethasone non-suppressors, but these statistics are comparable to adults (Kaufman et al., 2001).

Indices of serotonergic sensitivity in depressed children and adolescents have rarely been characterized. Peripheral prolactin levels negatively correlate with degree of depression and suicidality in adults (Maes et al., 1993) and children (Birmaher et al., 1997; Kaufman et al., 1998), and thus serve as a useful measure. Following serotonergic stimulation, two studies have found that children and adolescents with depression secreted more prolactin, suggesting serotonergic dysregulation (Ryan et al., 1992). However, findings of diminished prolactin response to clomipramine challenge (Sallee et al., 2000) and comparable baseline levels of blood plasma prolactin secretion across depressed, typical, and psychiatric control children (Hardan et al., 1999) illuminate the need to ascertain the precise nature and extent to which serotonergic mechanisms are associated with depression in children and youth.

3.2. Antidepressant effectiveness in childhood depression

Evidence-based pharmacotherapy for childhood depression has been relatively elusive until recently. Empirically, the tricyclic antidepressants (TCA’s) have little to no efficacy whereas the SSRI’s have been shown to be efficacious in the treatment of acute depression, similar to that observed in adults (Ryan, 2003). These findings parallel the higher prevalence of SSRI’s versus TCA’s at the national level (Martin and Leslie, 2003). Similar to the MTA, a large NIMH-funded study is currently underway (Treatment for Adolescents With Depression Study or TADS; (Anon., 2003) to ascertain the effectiveness of a SSRI (fluoxetine) compared to three other treatments (cognitive-behavioral therapy (CBT), SSRI + CBT, and pill placebo) for 432 adolescents aged 12–17 years with major depression.

Treatment for these early onset cases has had limited success. In a earlier series of studies, only 56% of children responded favorably to an SSRI versus 33% placebo response; these findings contrast with reports as high as 78% successful treatment response in adults versus a 44% placebo response; (Emslie et al., 1997; Emslie et al., 1998). The treatment refractory nature of childhood depression raises the issue of whether childhood depression represents a more severe form of adult major depressive disorder, although currently this tenet is not believed to be the case (Kaufman et al., 2001). An alternative hypothesis is that the current intervention strategies (i.e., SSRI’s) actually worsen the course of this disorder by altering the developmental trajectory of the serotonin system.

3.3. Childhood depression, SSRI’s, and suicidality

Today, SSRI’s are within the armamentarium of first-line psychotropic drugs available to clinicians in the treatment of childhood depression, which is supported by research regarding their effectiveness (Ryan, 2003). Because depression is a significant risk factor for suicide, prevention of suicide in children and adolescents necessitates effective treatment of depressive symptoms (Olsson et al., 1998; Pelkonen and Marttunen, 2003). Anxiety has also been associated with suicidality in children and adolescents (Mattison, 1988; Pfeffer, 1989). As with all drugs, potential adverse events associated with SSRI’s need to be acknowledged, including emotional, behavioral, and cognitive effects (Wilens et al., 2003).

Recently, a possible role for SSRI’s as an increased risk factor for suicide in children and adolescents with depression has been articulated. In June 2003, Britain’s Medicines and Healthcare products Regulatory Authority (MHRA)
advised clinicians that paroxetine (Paxil), a SSRI, should not be used in children and adolescents under the age of 18 years to treat depression because data from newer clinical trials do not demonstrate efficacy in depression in this age group. More alarmingly, risk of self-harm and potentially suicidal behavior increased 1.5–3.2-fold in the paroxetine group compared to the placebo group. Subsequently, the MHRA reviewed and banned the pediatric use of six other SSRI’s, but exempted fluoxetine (Prozac). In the US, fluoxetine is the only SSRI reviewed by the FDA that has received approval for pediatric use, although the others are often used “off label” by clinicians (i.e., sertraline, paroxetine, citalopram, venlafaxine, nefazodone, and mirtazapine). Following the MHRA’s advisory on paroxetine, the FDA issued its own public health advisory, stating that: “Although the FDA has not completed its evaluation of the new safety data, the FDA is recommending that Paxil not be used in children and adolescents for the treatment of Major Depressive Disorder.” A task force of the American College of Neuropsychopharmacology (ACNP) consequently evaluated the safety and efficacy of SSRI’s for treating depression in children and adolescents and concluded that SSRI’s do not increase the risk of suicidal thinking or suicide attempts and that the benefits of SSRI’s for treating childhood depression outweigh the risks of suicidal behavior. In February 2004, the FDA Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee held a meeting to consider the emergence of suicidality in the course of treatment of pediatric patients being treated for depression. At that meeting, a position statement from the American Academy of Child and Adolescent Psychiatry supported the ACNP task force conclusions and implicated depression itself as the most likely cause of suicide. Preliminary clinical findings suggest that cortisol and growth hormone levels during adolescence are associated with suicidal behavior during early adulthood. Mathew et al. (Mathew et al., 2003) found that adolescents with depression, who later made suicide attempts, appear to display significant elevations of cortisol prior to sleep onset, a time when the hypothalamic-pituitary-adrenal (HPA) axis is normally most quiescent. In a sample of adolescents who had experienced at least one lifetime major depressive episode during follow-up as young adults, the subgroup who eventually made suicide attempts secreted significantly greater amounts of growth hormone during the first few hours of sleep (Coplan et al., 2000).

3.4. Development of the serotonin system

Very little is known about neuropharmacological aspects of normal serotonin development during the periaadolescent period. Prior to the onset of puberty, the second and third week of life contain a number of transient events in serotonin innervation. Within the basal forebrain, serotonin forms exuberant synapses between birth and 14 days of age, during which the number of serotonin-labeled varicosities rises from 21.3% to 42% of values at birth (Dinopoulos et al., 1997). These varicosities then decrease to 17.1% during the third week, before rising again to 46% in adulthood. This second rise, which could also peak further during adolescence, is hypothesized to influence the functional state of their targets. This rising and falling pattern of innervation may be region-specific, as we found that serotonin innervation of the amygdala peaks at 60 days of age and prunes during adulthood (Andersen and Teicher, 1998). 3H-paroxetine binding, a 5-HT transporter ligand indicative of changes in 5-HT innervation, continues to increase in the fronto cortex into adulthood (Moll et al., 2000). Other changes include the transient expression of the serotonin 5-HT7 receptor in striatum before postnatal day 15, which is virtually absent by 21 days and adulthood (Vizuete et al., 1997), and a transient decline in serotonin utilization in the nucleus accumbens during adolescence that reverts to prepubertal levels in adulthood.

Genetic manipulations, including knockouts and inducible knockouts, will tremendously increase our knowledge about the role of serotonin in depression and anxiety during development. For example, knockout mice that lack 5-HT1B receptors show more impulsivity (a characteristic associated with violent suicide), including impulsive aggression, faster acquisition of cocaine self-administration, and increased ingestion of alcohol relative to wild-type mice (Brunner and Hen, 1997). The 5-HT1A receptor is believed to play a critical role in the expression of anxiety during development (Parks et al., 1998; Gross et al., 2002). Gross and colleagues (Gross et al., 2002) found that an anxious phenotype could be ameliorated if 5-HT1A receptors are present before 21 days of age in mice. If the receptor is not present after this developmental age, mice exhibit anxiety for the rest of their lives. The 5-HT transporter is another possible putative factor that requires further scientific scrutiny (Arango et al., 2002; Purselle and Nemeroff, 2003). Taken together, these data show that the presence, absence, or timing therein within the serotonin system can have dramatic consequences in the behavior of the adult animal that are consistent with depression and anxiety.

3.5. Antidepressant action and enduring effects of juvenile exposure

Antidepressants are believed to exert their therapeutic actions by increasing the availability of serotonin and noradrenaline within the synapse. This increase, in turn, results in postsynaptic receptor sensitization secondary to autoreceptor desensitization and elevated extracellular levels of serotonin (Hjorth et al., 2000; Newman et al., 2000). Changes in serotonin release are most likely mediated by the serotonin autoreceptor system, which is believed to slowly desensitize following chronic antidepressant treatment (Blier et al., 1987; Blier and Bouchard, 1994; Blier and Ward, 2003). Initially, fluoxetine inhibits hippocampal cell
firing in a dose-dependent manner via its 5-HT\textsubscript{1A} effects on the raphe (Sprouse et al., 2001). With time, chronic fluoxetine (10 mg/kg) reduces GTP-gamma S binding induced by 8-OHDPAT in dorsal raphe nucleus (DRN), resulting in a desensitization of autoreceptor regulation of DRN firing rate (Elena Castro et al., 2003). Numerous studies have shown that a desensitization of the somatodendritic 5-HT\textsubscript{1A} autoreceptor produces increases in serotonin release in the terminal fields (Moret and Briley, 1990; Sprouse et al., 2001). Furthermore, 5-HT\textsubscript{1B} autoreceptors in the terminal fields (Malagie et al., 2001; Malagie et al., 2002), including the frontal cortex (Blier et al., 1984; O’Connor and Kruk, 1994; el Mansari et al., 1995; Moret and Briley, 2000; Newman et al., 2000), desensitize, which is believed to underlie the proposed therapeutic action of the drugs—the sensitization of postsynaptic serotonin receptors (Blier and Bouchard, 1994; Elena Castro et al., 2003).

Chronic exposure to antidepressants during development is a remarkably understudied area of research, particularly given our knowledge that enduring effects exist that are both age- and region-dependent. To demonstrate the importance of the timing of exposure for lasting effects, pre- and postnatal antidepressant exposure differ. For example, prenatal exposure to fluoxetine decreases the density of the serotonin transporter (Montero et al., 1990), cortical phosphoinositide hydrolysis (Romero et al., 1993), and serotonin content in the cortex (Cabrera-Vera et al., 1997) of pre-pubescent rats. These effects wane with adulthood. In contrast, the effects of juvenile exposure to tricyclic antidepressants endure into adulthood and have been well characterized in the clomipramine animal model of depression (Vogel et al., 1990a,b,c; Feenstra et al., 1996; Andersen et al., 2002b).

Stemming from initial studies by Mirmiran and colleagues, which demonstrated increased REM sleep in adult rats (Mirmiran et al., 1981; Mirmiran et al., 1983; Mirmiran et al., 1985; Vogel et al., 1990a,b,c), additional depressive behavioral symptoms, including diminished pleasure-seeking (Vogel et al., 1990a,b,c), decreased aggressiveness (Vogel et al., 1988), impaired sexual activity (Neill et al., 1990; Bonilla-Jaime et al., 1998), anxiety-like behavior (Andersen et al., 2002a), and increased immobility in a forced swim paradigm (Marvan et al., 1996), have been documented. We have found that early clomipramine exposure increases anxiety-like behavior (Andersen et al., 2002a), which is highly correlated with changes in serotonin in the amygdala (Andersen and Teicher, 1999; Yannielli et al., 1999).

The clomipramine model of depression is not restricted only to tricyclic antidepressant exposure. One study mimicked a number of these characteristics with the juvenile administration of a serotonin agonist, citalopram (Hyttel, 1978). Furthermore, the enduring effects of juvenile fluoxetine exposure on neuroanatomy have been documented. Consistent with the “equal, but opposite” hypothesis, Norrhelm and Ouimet (2000) found that chronic exposure to fluoxetine prevents the normal development of dendritic spines in the hippocampus. Spine density in adulthood in treated rats was approximately equal to the density present when they had completed treatment as juveniles, suggesting that further spine development was arrested. However, these researchers failed to find similar changes with fluvoxamine. In cell culture, elevated levels of serotonin decrease neuronal branching (Whitaker-Azmitia and Azmitia, 1986; Whitaker-Azmitia, 1991), which contrasts findings obtained from adult exposure studies showing antidepressant-enhanced neurogenesis (Gould, 1999; Malberg et al., 2000; Lee et al., 2001). Currently, no data are available on juvenile antidepressant exposure on serotonin and norepinephrine function later in life. Studies on long-term antidepressant effects of SSRI’s following withdrawal in adults have produced variable results that are highly dependent on the brain region examined (Sarkissian et al., 1990; Trouvin et al., 1993). For example, chronic fluoxetine (30 mg/kg; 3 days) produces an increase in serotonin levels in the frontal cortex after withdrawal (Sarkissian et al., 1990). In contrast, smaller doses produce a transient decrease in serotonin levels (Trouvin et al., 1993). Taken together, juvenile exposure to tricyclic and SSRI antidepressants causes lasting decrements in the serotonin system in adulthood. In the handful of studies that have been conducted on this issue in adults, the results indicate a return to baseline levels within a few weeks of discontinuation.

3.6. Norepinephrine: the unknown frontier

As discussed above, both stimulants and antidepressants alter the course of development. Common to both classes in most (but not all) of the specific medications discussed is norepinephrine. MPH, amphetamine, the less-specific antidepressants, TCA and venlafaxine, and the noradrenergic drugs, atomoxetine and reboxetine, all have activity at the noradrenergic uptake carrier. Interactions with both dopamine and serotonin are common, and synergistically increase their therapeutic influence (Szabo et al., 2000; Hopwood and Stamford, 2001; Szabo and Blier, 2001; Linner et al., 2004). For example, agents that block both serotonin and norepinephrine (e.g., venlafaxine) also have clinical utility possibly by increasing serotonin release more than fluoxetine alone (Artigas et al., 2002). Research on the enduring actions of juvenile exposure to noradrenergic agents is sparse, but represents an important avenue of future exploration.Seminal preclinical research demonstrates that the expression of receptors and phospholipids vitally depends on norepinephrine levels (Deskin et al., 1981). These same authors have shown that ornithine decarboxylase activity will rise and fall with changing norepinephrine levels during periods when noradrenergic system development is most active (Morris et al., 1983). Taken together, these data imply that the immature noradrenergic system is also exquisitely sensitive to changing levels of norepinephrine during early postnatal development.
4. Hope on the horizon

Disease-related changes in developmental trajectories have already been proposed for a number of psychiatric disorders: (1) schizophrenia may result from a delay in the elimination of dopaminergic synapses (Giedd et al., 1999a,b; Rapoport et al., 1999); and (2) bipolar disorder may result from precocial pruning of synapses (Saugstad, 2001). However, inherent in their expression is the presence of a strong underlying genetic predisposition and a second hit from the environment for their expression. The converse of a second hit hypothesis of disease is a second chance model of intervention. Lessons learned from the adverse consequences of early drug exposure could, in turn, be used to identify and/or develop better models of treatment. Amongst the questions we should now be asking is whether the decline of ADHD symptoms in adulthood that occurs in approximately 70% of cases (Klein and Mannuzza, 1991; Teicher et al., 1997) is the result of a positive effect of drug exposure on altering an abnormal developmental trajectory. If so, then what are the specific factors that influence this process? Similarly, what are the effects of antidepressant therapy? Increased depression? Suicide risk?

Pharmacological tools represent some of the best approaches we have. Their effectiveness in adult populations speaks to the underlying neurobiology of the disease, especially its complex nature. Awareness of this complexity is vitally important given that rarely is a single neurotransmitter system implicated in any of the above-mentioned disorders; but, in a similar vein, the majority of the treatments is not specific either. Individually tailored psychotropic drugs that simultaneously ameliorate childhood symptoms effectively and foster normal brain maturation will hopefully be a reality in the near future.

5. Conclusions

The growing prevalence of psychotropic drugs to treat childhood psychiatric disorders is undeniable. As such, clinical researchers have begun to question the impact of these agents on the developing brain (Vitiello, 1998; Andersen, 2003). For example, Pine (2002) recently examined the safety and efficacy of SSRI’s in the short-term treatment of childhood depression and anxiety, in light of their potential risks and benefits with long-term use, through the lenses of longitudinal outcome, neuroscience, and psychopharmacology. He concludes that antidepressant therapy should be used as needed and that use be discontinued as soon as symptoms stabilize. In parallel, developmental neuroscientists are in an equivalent and unique position to substantially contribute to a better understanding of how drug effects can influence—both positively and negatively—neurodevelopment and behavioral health later in life. Certainly, there is room to grow in understanding the trophic effects of neurotransmitters in the juvenile animal and their long-term impact on developmental trajectories.

References


