A Biological/Genetic Perspective: The Addicted Brain

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Introduction

Exposure to medications, chemicals, infectious disease, or environmental agents (i.e., potential teratogens) presents a significant health risk during human development, particularly during critical periods of organ and system development. Risk of exposure during the critical periods of embryonic and fetal development has been well documented, but recent evidence suggests that critical periods of organ development, especially brain development, extend into childhood and adolescence. Given the extended period of brain development, risks associated with exposure to teratogens having direct effects on the brain (i.e., psychoactive drugs) may also extend into childhood and adolescence. This chapter examines the health risks associated with developmental exposure to psychoactive drugs of abuse.

Exposure to psychoactive drugs can impact normal biological development in ways that are similar to other teratogens. However, psychoactive drugs can also influence brain and behavioral functions through direct pharmacological modula-

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tion of neuronal function and structure. As such, the developmental risk related to exposure to psychoactive drugs is exacerbated by the potential for adverse consequences related to the neuropharmacological effects of the drugs occurring during critical periods of development. Concerns are further heightened if one considers frequency of exposure. Some psychoactive drugs function as reinforcers and engender repeated drug-taking behavior, and increased frequency of neuropharmacological exposure exacerbates risk of developmental problems.

Risk of prenatal exposure to psychoactive drugs of abuse is substantial, given that rates of drug use in the general population are highest among individuals of reproductive age and significant drug use is reported among pregnant women (e.g., 11.5% of pregnant adolescent women report past month alcohol use, and 23% report past month use of tobacco) (Oh, Reingle Gonzalez, Salas-Wright, Vaughn, & DiNitto, 2017). Exposure to psychoactive drugs of abuse can occur postnatally through passive exposure from environmental sources (e.g., tobacco smoke, methamphetamine production). Developmental exposure to drugs of abuse among children and adolescents has escalated in the past decades as drugs have become increasingly available to younger age groups and experimentation has increased. Furthermore, genetic, developmental, and other neurobiological factors influence individual sensitivity to the reinforcing and other neuropharmacological effects of psychoactive drugs (Chambers, Taylor, & Potenza, 2003). In combination with cultural, community, peer, and family influences, enhanced sensitivity to the reinforcing and other pharmacological effects of drugs place some children and adolescents at increased vulnerability for repeated drug use (e.g., Kelly et al., 2006; Stoops et al., 2007) and for the development of heavy use, abuse, and dependence (Chaloupka & Johnston, 2007). Individual differences in sensitivity to the neuropharmacological effects of drugs can increase the risk of adverse health consequences associated with drug use, including engaging in other risky behaviors (e.g., sexual behavior, driving behavior, self-injurious behavior, and gambling), as well as adverse short- and long-term social (education, peer and family relations), medical (mental and physical health), and legal consequences. Finally, evidence links exposure to psychoactive drugs of abuse during critical periods of development to enhanced sensitivity to the reinforcing and other neuropharmacological effects of drugs, which, in turn, leads to enhanced likelihood of repeating drug use, followed by further enhancement of sensitivity (e.g., Derauf, Kekatpure, Neyzi, Lester, & Kosofsky, 2009; Glantz & Chambers, 2006).

Neurodevelopment

Substantial neuronal growth occurs during prenatal embryonic development. However, critical periods of neurogenesis and synaptic remodeling also occur in response to environmental experiences and continue after birth and throughout childhood and adolescence (e.g., Tau & Peterson, 2010). For example, maturation of the mesolimbocortical system—a pathway often implicated in the rewarding

effects of drugs of abuse—continues during childhood and early adolescence, while inhibitory functions of the orbitofrontal cortex—a brain region shown to be involved in self-regulation—continue to develop into the early twenties (e.g., Galvan et al., 2006; Nigg, 2017; Steinberg, 2010). High levels of impulsiveness and risk-taking behavior among adolescents have been linked to asynchronous development of reward and inhibitory functions, with the alerting and motivating functions of the dopaminergic reward pathway emerging during early adolescence, while the inhibitory processes of the frontal cortex that hold these functions in check may not become fully mature until early adulthood (Crews, He, & Hodge, 2007). Risk associated with psychoactive drug exposure during critical periods of prenatal and postnatal human brain development has been well recognized. However, since periods of critical development continue throughout childhood and adolescence, it is important to recognize that risks to optimal brain development associated with psychoactive drug exposure extend well beyond the period of embryonic growth (Tau & Peterson, 2010).

Pharmacology

Drugs enter the body through several routes: parenteral (intravenous, intramuscular, and subcutaneous), enteral (oral, sublingual, and rectal), inhalation, intranasal, intrathecal, transdermal, and topical. Research has established that a rapid rise in plasma levels, quick entry into the brain, and relatively short-acting behavioral effects increase the reinforcing effects and abuse liability of a compound (Feldman, Meyer, & Quenzer, 1997). Drugs enter the bloodstream and reach the brain most rapidly when administered intravenously or via inhalation (i.e., smoking).

Drug action diminishes through metabolic and excretory processes. Body mass, total body water, amount of body fat, and maturity of liver enzymes involved in drug metabolism influence the rate at which a drug is metabolized and eliminated. Each of these factors varies as a function of stage of development. For example, children and adolescents are more vulnerable to some drug effects because they do not have the ability to clear drugs from the body as efficiently as adults (e.g., Holford, Heo, & Anderson, 2013). The implications of a slower metabolic transformation are that the active drug or active metabolites remain in the bloodstream for a longer period of time and often increase the duration of the drug's effects. Blood level engendered by a dose of drug is also an important determinant of the effect of a drug (e.g., blood alcohol levels and performance impairment). Body mass is an important determinant of blood levels, such that blood concentration is proportional to body mass. Because children and adolescents are typically smaller than the average adult, drug doses typically used by adults will engender relatively higher blood concentrations in children and adolescents than in adults. For example, when a 200 lb. (or 90.72 kg) adult consumes 100 mg of caffeine, a dose of 1.10 mg/kg of body weight is consumed. If a 90 lb. (or 40.82 kg) adolescent consumes the same beverage containing 100 mg of caffeine, a dose of 2.45 mg/kg, over two times the relative dose consumed by the adult man, is consumed.

Relative drug dose determined by body mass is relevant when examining the effects of drugs in the fetus and infant. Drugs pass from mother to fetus through the vasculature of the placenta and to the newborn through breast milk. Many compounds that the mother consumes during pregnancy cross the placenta and enter the bloodstream of the fetus (Myllynen, Pasanen, & Pelkonen, 2005). The total dose of the drug that reaches the fetus is dependent on the dose of the drug ingested by the mother, the manner in which the drug is excreted, and the metabolic rate and pathway of the drug (Ostrea, Mantaring, & Silvestre, 2004). Several reviews detail the effects and risks associated with placental transfer of a wide range of licit and illicit drugs (Briggs, Freeman, & Yaffe, 1998; Garland, 1998; Ostrea et al., 2004). Mothers can also expose infants to drugs through breast milk. The total dose that reaches the infant depends on the dose the mother ingested, the duration of the drug regimen (occasional vs. consistent use), the route of administration (drugs that enter the mother's system parenterally are typically less concentrated in the breast milk than those administered orally), the pharmacokinetics of the drug (drugs with longer half-lives have greater potential to collect in significant amounts in milk), and the infant's ability to absorb, metabolize, and excrete the drug, with older infants being able to process most drugs more efficiently than premature or younger infants (Ostrea et al., 2004).

Neuropharmacology

Neuronal communication in the brain occurs through an electrochemical process, with electrical impulses in a neuron modulating the release of chemicals [i.e., neurotransmitters, such as dopamine, serotonin, endogenous opiates, *N*-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), and acetylcholine]. Released chemicals diffuse across small spaces (i.e., synapse) between adjacent neurons, and binding of these neurochemicals to proteins (i.e., receptors) on the membranes of the adjacent neurons leads to modulation of electrical signals and other activities in adjacent neurons. Action by neurotransmitters in the synapse is then terminated by metabolic enzymes, or reabsorption into presynaptic neurons. Psychoactive drugs capitalize on this system, modulating action at the receptor level or altering the manner in which neurons regulate neurotransmitters. Homeostatic functions keep a regular balance of neurotransmitter release and inhibition, and upset of this balance by drugs can lead to effects on hormonal action, learning, memory, mood, reward, and behavior.

Most drugs of abuse have direct or indirect effects on neurons utilizing dopamine as the neurotransmitter signal, particularly those in the dopamine-rich mesolimbocortical system (e.g., caudate/putamen, nucleus accumbens, tuberculum olfactorium, and prefrontal and frontal cortex), sometimes referred to as the dopamine reward pathway. Increased activation of dopamine release (i.e., potentiation) in this pathway is a common neuropharmacological mechanism of action of the drugs that function as reinforcers (i.e., drugs with abuse liability). The mesolimbocortical

system is still undergoing development in childhood and adolescence, and it has been argued that enhanced stimulation of this pathway during development, as would occur during exposure to drugs of abuse, can cause permanent changes in the sensitivity of these regions (e.g., Andersen & Navalta, 2004).

Summary

Prenatal, childhood, and adolescent stages are times of rapid neurodevelopment with synaptic connections continually forming and brain structures constantly developing. Exposure to drugs and other teratogens during these critical periods of development has both short- and long-term health consequences. Psychoactive drugs are of particular concern, given that these compounds have direct effects on brain function and engender both short- and long-term effects on the brain and behavior, with risk of exposure elevated among psychoactive drugs of abuse.

Caffeine

Caffeine is the most widely consumed psychoactive drug among adults and children (Warzack, Evans, Floress, Gross, & Stoolman, 2011). Of increasing concern is the use of energy drinks by children, adolescents and young adults who are at particular risk for harmful effects (Seifert, Schaechter, Hershorin, & Lipshultz, 2011).

Mechanisms of Action

Caffeine (1, 3, 7-trimethylxanthine) is a purine alkaloid found in the beans, leaves, and fruits of over 60 plants (Weinberg & Bealer, 2001). Effects in the central nervous system (CNS) occur primarily through binding with and blocking the membrane proteins (i.e., receptors) that are activated by the endogenous neurotransmitter adenosine (Daly & Fredholm, 1998; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). Adenosine is an inhibitory neuromodulator that increases sedation and acts as an anticonvulsant. In addition, adenosine decreases blood pressure, respiration, gastric secretions, diuresis, and lipolysis (Daly & Fredholm, 1998; Garrett & Griffiths, 1996). By blocking adenosine receptors, caffeine antagonizes the typical effects of adenosine, such as sedation, which results in the stimulant-like effects of the drug.

Caffeine also has indirect agonist effects on dopamine activity, which is related to its adenosine receptor blockade. Heavy concentrations of adenosine receptors are found in the dopamine reward pathway (Daly & Fredholm, 1998; Ferre, Euler, Johansson, Fredholm, & Fuxe, 1991; Ferre, Fuxe, von Euler, Johansson, &

Fredholm, 1992). Adenosine receptors regulate dopamine release as well as GABA neuron activation; GABA serves an inhibitory role in the dopamine reward pathway. By antagonizing adenosine, caffeine indirectly enhances dopamine release and diminishes the inhibitory functions of the GABA system (Daly & Fredholm, 1998; Ferre et al., 1992; Garrett & Griffiths, 1996).

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Caffeine Exposure

On average, a mug of drip-brewed coffee contains ~100 mg of caffeine. A similar size serving of tea contains 80 mg, and a 12 oz. serving of a caffeinated soda contains ~40 mg. The average daily amount of caffeine consumption for adults is ~230 mg/day (3.3 mg/kg/day), with 30% of adults consuming more than 500 mg/day (7.1 mg/kg/day; DSM-IV). Caffeine is the psychotropic drug most commonly consumed by pregnant and nursing women, with 60–68% of this population consuming moderate amounts (100–200 mg) of caffeine daily (Frary, Johnson, & Wang, 2005; Pirie, Lando, Curry, McBride, & Grothaus, 2000). While mean daily caffeine consumption for children and adolescents has been estimated to range from 37 to 63 mg/day (Morgan, Stults, & Zabik, 1982; Valek, Laslavić, & Laslavić, 2004), 20–25% of this population consume over 100 mg/day, with occasional reports of consumption of 290–500 mg/day or more (Leviton, 1992; Rapoport, Berg, Ismond, Zahn, & Neims, 1984). Caffeine consumption does not vary as a function of gender, but differences have been reported among racially classified groups (Arbeit et al., 1988; Leviton, 1992). It is important to point out that soft drink consumption, which is the major source of caffeine in school-aged children, has more than tripled since 1970 (Story & Neumark-Sztainer, 1998; Valek et al., 2004). Sales of caffeinated "energy" drinks, which contain 2–3 times the amount of caffeine per given volume compared to conventional caffeinated soft drinks, are increasing among adolescents and young adults (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007).

In the third trimester of pregnancy, caffeine's half-life (amount of time required to eliminate 50% of the drug concentration) increases from 2–6 to 10–20 h (Brazier, Ritter, Berland, Khenfer, & Faucon, 1983; Knutti, Rothweiler, & Schlatter, 1982). In utero, caffeine is passed from mother to child through the placenta, readily entering the fetal bloodstream, such that ~75% of babies are born with detectable levels of caffeine in their blood (Brazier & Salle, 1981; Dumas et al., 1982). After birth, it is also passed via breast milk to nursing infants (Benowitz, 1990; Julien, 2001). From prenatal stages to at least 3 months of age, the hepatic enzymes necessary to metabolize the drug are absent or immature, causing the drug's half-life to be anywhere from 32 to 149 h (Parsons & Neims, 1981). As such, blood levels of caffeine may be elevated in the neonate and newborn in relation to levels seen in adolescents and adults. After the metabolic enzymes develop, metabolic rates approximate that of adults (James, 1991).

The degree to which caffeine exposure affects the health and well-being of a fetus, neonate, newborn, or infant remains unclear. The research literature on this topic is vast and equivocal, with reports ranging from virtually no adverse health consequences (Giannelli, Doyle, Roman, Pelerin, & Hermon, 2003; Leviton & Cowan, 2002; Savitz, Chan, Herring, Howards, & Hartmann, 2008) to early term birth and increased risk of miscarriage (Bech, Nohr, Vaeth, Henriksen, & Olsen, 2005; George, Granath, Johansson, Olander, & Cnattingius, 2006; Rasch, 2003). More recently, Galéra et al. (2016) found that prenatal caffeine exposure was negatively associated with full scale and performance IQ at age 5.5 years. This relationship was maintained even when controlling for tobacco use. Earlier studies have not found associations between intrauterine caffeine exposure and behavioral changes in early childhood (Loomans, 2012).

A variety of studies have examined the effects of caffeine in children and adolescents. In normal children and adolescents, low doses of caffeine (3 mg/kg) have been reported to improve attention and performance of vigilance tasks, reduce reaction time, improve manual dexterity, improve memory, reduce errors of omission on continuous performance tests, and increase speech production (Castellanos & Rapoport, 2002; Elkins et al., 1981; Hughes & Hale, 1998; Leon, 2000; Leviton, 1992; Rapoport, Elkins, Neims, Zahn, & Berg, 1981; Stein, Krasowski, Leventhal, Phillips, & Bender, 1996), particularly when performance is less than optimal due to boredom or fatigue. Caffeine use is associated with later sleep times, less time in bed, and changes in sleep architecture (e.g., decreased depth of sleep, Aepli, Kurth, Tesler, & Huber, 2015), and poorer academic performance (Dimitriou, Cornu Knight, & Milton, 2015). Higher doses of caffeine can also be associated with inattentiveness, restlessness, nausea, stomachache, and dysphoria and depression—including nervousness, jitteriness, stress, and anxiety (Hughes & Hale, 1998; Orbeta, Overpeck, Ramcharran, Kogan, & Ledsky, 2006; Pollak & Bright, 2003; Richards & Smith, 2015; Sojar et al., 2015). Symptoms of caffeine withdrawal (Bernstein et al., 1998; Hughes & Hale, 1998) and caffeinism (Castellanos & Rapoport, 2002) have been noted in children and adolescents. In general, these effects are similar to those reported in adults.

There is evidence that heavy caffeine use is associated with drug use and other problem behaviors in children and adolescents (Tennant & Detels, 1976). In particular, moderate and heavy energy drink use in middle and high school predicted lifetime alcohol, tobacco, and other drug use (Polak et al., 2016). It is not known whether behavioral problems in children and adolescents who consume large amounts of caffeine are due to caffeine, or whether children and adolescents with these problems consume large amounts of caffeine in order to self-medicate their symptoms (Leviton, 1992).

Caffeine may interact with and enhance the effects of other drugs of abuse. For example, caffeine has been found to enhance the reinforcing and stimulant subjective effects of nicotine in adult cigarette smokers (Jones & Griffiths, 2003). Of particular concern is the increase in emergency room presentations related to energy drink toxicity frequently in combination with alcohol and other drugs of abuse (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013a).

Implications

Levels of caffeine exposure during human development are higher than any other psychoactive drug. Caffeine levels during prenatal development and for the first several months after birth are elevated due to the absence of enzymes required for efficient caffeine metabolism. Caffeine intake in sodas and energy drinks is increasing among children and adolescents, and heavy intake has been linked to drug use and other problem behaviors. The American Academy of Pediatrics (2011) recommends that energy drinks should "never be consumed" by children or adolescents.

Nicotine

Nicotine is consumed in tobacco cigarettes, chewing tobacco, hookah, nicotine gums and patches, and electronic cigarettes. Use of tobacco cigarettes, the most widespread form of nicotine delivery, cause approximately one in five deaths in the USA every year (US Department of Health and Human Services, 2014). Nicotine has been described as one of the most addictive substances of abuse based on observations that close to 32% of individuals who "ever" smoke go on to develop nicotine dependence (Anthony, Warner, & Kessler, 1994). The next closest drug is heroin, with 23% of ever users developing dependence, followed by cocaine at 17%, and alcohol at 15%. Recent prevalence estimates of daily tobacco cigarette use among 12th graders have decreased from approximately 21% in 1980 to 7% in 2015 (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). There are also large gender differences in smoking rates. In 1980, it was estimated that 41.2% of men and 10.6% of women used cigarettes daily, while in 2015 an estimated 31.1% of men and 6.2% of women are daily cigarette users (Ng et al., 2014). The majority of adult smokers initiate tobacco use before age 18, and the earlier the age of smoking initiation, the greater the likelihood of lifetime use (Kopstein, 2001). Although tobacco cigarette use has decreased over time, consumption of nicotine in electronic cigarettes has rapidly increased over the past few years, with recent estimates of past month use of electronic cigarettes among emerging adults as high as 41% in 2013 (Ramo, Young-Wolff, & Prochaska, 2015). Of concern, neither the behavioral nor the health effects of electronic cigarette use are well characterized at the present time.

Mechanisms of Action

Nicotine binds to receptors widely distributed throughout the brain that are normally bound by the endogenous neurotransmitter acetylcholine. There are several subtypes of "nicotinic acetylcholine" receptors, composed of differing arrangements of alpha and beta protein subunits. Nicotinic acetylcholine receptors exert a

variety of effects in the CNS, including modulation of dopamine function. As with other drugs of abuse, nicotine modulation of the dopamine reward pathway is considered a primary mechanism for its abuse liability (Picciotto & Corrigall, 2002). The alpha-4, beta-2 nicotinic acetylcholine receptor type is most closely linked with dopamine modulation and nicotine dependence (Tapper et al., 2004). Nicotine enhancement of dopamine neurotransmission is believed to be responsible for tolerance to nicotine and for the development of conditioning to environmental cues associated with smoking behavior (Liu et al., 2003; Maskos et al., 2005; Picciotto, Zoli, & Changeux, 1999; Pidoplichko et al., 2004; Salminen et al., 2004; Tapper et al., 2004).

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Nicotine Exposure

Approximately 23% of pregnant adolescents report past month use of tobacco (Oh et al., 2017). Rates of smoking identified with surveys are generally lower than those identified when quantitative measures of smoking (e.g., salivary cotinine) are used to determine smoking rates (Walsh, Redman, & Adamson, 1996), suggesting that the 23% frequency could be an underestimate of the true rate.

In utero exposure to nicotine has important implications for brain development. Nicotine receptors appear by the end of the first month of human fetal life and are critical for brain growth and neuronal connectivity, including modulation of nerve growth and formation of new synaptic connections between neurons in the brain (Hellstrom-Lindahl, Seiger, Kjaeldgaard, & Nordberg, 2001). Animal studies have found that prenatal and postnatal nicotine exposure is associated with alterations of a variety of endogenous neurotransmitter systems mediated by dopamine, norepinephrine, and serotonin (Muneoka et al., 2001; Richardson & Tizabi, 1994; Slotkin, Pinkerton, Auman, Qiaio, & Seidler, 2002; Xu, Seidler, Ali, Slikker, & Slotkin, 2001). Research has shown that the thickness of regions in the cortex (orbitofrontal, middle frontal, and parahippocampal) associated with cognition and social control is reduced in adolescents exposed to maternal smoking (Toro et al., 2008). There is also evidence that offspring of mothers who smoked cigarettes during pregnancy have children with reduced total brain volume later in childhood (El Marroun et al., 2013).

In utero exposure to nicotine has important implications for behavioral development. Prenatal nicotine exposure is associated with the development of altered patterns of behavior during early postnatal life and later in childhood (Law et al., 2003; El Marroun et al., 2013). For example, children exposed in utero are more likely to be impulsive, hyperactive, oppositional, and have lower language skills than their unexposed peers (Day, Richardson, Goldschmidt, & Cornelius, 2000; Faden & Graubard, 2000; Fried & Watkinson, 1990; Wakschlag, Leventhal, Pine, Pickett, & Carter, 2006). Multiple studies suggest that these effects continue to be expressed during adolescence. Children of mothers who smoked during pregnancy are at greater risk for a broad range of mental health problems (Goodwin et al.,

2013). Specifically, in utero exposure increases the risk of developing both internalizing and externalizing disorders (e.g., mood disorders, conduct disorder) known to be risk factors for the emergence of adolescent experimental and persistent smoking (Fried & Watkinson, 2001; Upadhyaya, Deas, Brady, & Kruesi, 2002). Postnatal environmental tobacco smoke exposure may also have an impact on child and adolescent brain and behavioral development (Okoli, Kelly, & Hahn, 2007), although disentangling postnatal and prenatal associations is methodologically difficult (Eskenazi & Castorina, 1999).

By the age of 10, nicotine-exposed offspring are more likely to have tried smoking, and smoking rates among the prenatally exposed remain higher during adolescence (Cornelius, Leech, Goldschmidt, & Day, 2000; Nichter, Nichter, Thompson, Shiffman, & Moscicki, 2002; Niemelä et al., 2017). Adult women exposed to tobacco in utero are four times more likely to be smokers than those who were not exposed (Kandel, Wu, & Davies, 1994). It is clear that there are multiple environmental, biological, and genetic factors that contribute to tobacco use, and many of these factors may also contribute to multigenerational tobacco use.

Research on the effects of nicotine use during pregnancy has focused primarily on nicotine delivered via tobacco cigarettes. Little is currently known, however, about the effects of electronic cigarette use during pregnancy. Due to the current lack of regulation on electronic cigarettes, there are a wide variety of undisclosed ingredients in their liquids, making it difficult to generalize about their health effects. Nonetheless, there is growing consensus that they typically contain fewer chemicals than tobacco cigarettes (e.g., Suter, Mastrobattista, Sachs, & Aagaard, 2015). Electronic cigarette liquids, however, usually contain nicotine, which is a known teratogen. As such, electronic cigarette use is not recommended during pregnancy.

Rates of nicotine dependence among adolescents have been difficult to determine, in part, because the criteria used to establish dependence among adults may not be as effective in assessing dependence among adolescents (Colby, Tiffany, Shiffman, & Niaura, 2000). Adolescents endorse more symptoms of dependence than do adults smoking the same number of cigarettes per day, suggesting that adolescents may be more sensitive to the effects of nicotine (Kandel & Chen, 2000). Kandel et al. (2005) found that various measures of nicotine dependence yielded different rates of dependence between adolescents and adults, especially at low levels of smoking. However, dependence rates became more consistent between adolescents and adults as the smoking rate approached one pack per day. In cross-sectional studies, withdrawal symptoms have been reported earlier in the course of tobacco use among adolescents than among adults, and may precede regular or daily use among adolescent smokers (DiFranza et al., 2007; O'Loughlin et al., 2003). It is possible that the reinforcing effects of nicotine are enhanced among adolescents, and that young smokers may develop tolerance and physical dependence more rapidly upon initiation of tobacco smoking than do adults. Based on when smoking is initiated and the associated adverse lifetime health consequences of tobacco use, nicotine addiction has been labeled a disease of adolescence (Kessler et al., 1997).

For at least some neurotransmitter systems (e.g., serotonin and acetylcholine), the CNS responses to nicotine during adolescence appear to be similar to those observed during other stages of life (Trauth, McCook, Seidler, & Slotkin, 2000; Xu et al., 2001). However, some unique nicotine effects occur during adolescence [i.e., effects that are different than those observed during either in utero or adult nicotine exposure (Slotkin, 2002)]. Laboratory experiments demonstrate differences between adolescent and adult behavioral responses to nicotine. Trauth, Seidler, and Slotkin (2000b), for example, gave nicotine to adolescent rats in a manner designed to mimic the effects of smoking over a period of days, then observed them in a novel environment while they performed a passive avoidance task. Contrary to effects seen in adult rats, nicotine decreased grooming behavior in the novel environment by adolescent females and enhanced passive avoidance behavior 24 h post-training, indicating differential effects of nicotine among adolescent rats compared to adults. Kota and Martin (2007), in a series of behavioral experiments with mice, found that adolescent mice exhibited nicotine-induced changes in receptor sensitivity and fewer withdrawal signs than did adult mice. A series of experiments by Faraday, Elliott, Phillips, and Grunberg (2003) demonstrated that behavioral sensitivity to nicotine in adult rats was increased by prior exposure to nicotine during adolescence. Timing of initial exposure also impacted rates of nicotine self-administration during adulthood, with adolescent-exposed rats self-administering more nicotine than did adult-exposed rats (Adriani et al., 2003; Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003).

Implications

There is considerable evidence indicating that risk for development of nicotine dependence is increased by nicotine exposure during early human development (Ginzel et al., 2007). Prenatal nicotine exposure engenders adverse behavioral outcomes that are associated with increased risk of adolescent smoking. Research demonstrates that adolescence is a critical time period during which nicotine exposure may permanently restructure the brain and increase lifetime risk of smoking. Environmental factors interacting with this biological vulnerability may set the stage for adult nicotine dependence and other psychopathology. Consequently, strategies and policies designed to limit exposure to nicotine during early life have the potential for prevention of significant adult morbidity and mortality.

Alcohol

Alcohol is widely used among American youth and threatens their health and safety. The Centers for Disease Control and Prevention (CDC) (2015a) reported that one in five youth between ages 12 and 17 reported past-year alcohol use. From 1996 to

2016, past month use reported by 8th, 10th and 12th graders through the Monitoring the Future (MTF) survey has shown a decline with percentage of use in 2016 noted at 7.3, 19.9 and 33.2, respectively (Johnston et al., 2016). That said, the 2015 Youth Risk Behavior Survey of high school students reported 8% drove after drinking and 22% rode in a car with someone who had been drinking alcohol (Kann et al., 2016). Motor vehicle accidents are the leading cause of death among teens. Between 2006 and 2010, average alcohol related deaths annually were greater than 4300 with more than 1500 associated with motor vehicle accidents (Centers for Disease Control and Prevention (CDC), 2013). In addition to physical injuries, adverse consequences related to excessive alcohol consumption include development of chronic diseases, including psychiatric disorders, neurologic impairment, cardiovascular disease, malignant neoplasms and fetal alcohol spectrum disorders (Cargiulo, 2007). Adverse social and cultural consequences of alcohol use are also apparent (National Institute on Alcohol Abuse and Alcoholism, 2004–2005). Early exposure to alcohol can have detrimental effects on future health. Fetal and infantile alcohol exposure is predictive of subsequent alcohol use during adolescence, and alcohol use during adolescence is associated with excessive alcohol use later in life (Spear, 2002; Spear & Molina, 2005). Onset of drinking alcohol before age 15 increases risk of abuse or dependency sixfold compared to those starting at the legal drinking age (Centers for Disease Control and Prevention (CDC), 2015a). Alcohol use during adolescence is also associated with elevated risks for liver disease and adverse endocrine and metabolic effects (National Institute on Alcohol Abuse and Alcoholism, 2004–2005).

Mechanisms of Action

Alcohol engenders multiple neurochemical effects and has a potent adverse impact on the developing brain. Changes in the integrity of the neuronal cell membrane occur during intoxication (Deitrich, Dunwiddie, Harris, & Erwin, 1989). Alcohol acts on multiple neurotransmitter systems, including NMDA, GABA, serotonin, and the endogenous opiate systems, with variability in the form and function of these neurotransmitter systems having a likely role in individual sensitivity to alcohol's effects (Charness, Hu, Edwards, & Querimit, 1993; Lesch, 2005; Wafford, Burnett, Harris, & Whiting, 1993). The NMDA and GABA systems modulate dopamine function, and alcohol modulates the dopamine reward pathway via its effects on NMDA and GABA receptors (Grobin, Matthews, Devaud, & Morrow, 1998; Verheul, van den Brink, & Geerlings, 1999; Zhang, Maldve, & Morrisett, 2006). The neurotoxic effects of acute and chronic alcohol exposure are also mediated via these mechanisms. Abstinence following heavy alcohol exposure (e.g., alcohol withdrawal) also has adverse effects on brain neurotransmitter systems and neuronal cell function (Grobin et al., 1998; Tsai et al., 1998).

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Alcohol Exposure

In utero alcohol exposure can have a profound impact on brain development. Approximately 50% of women above the age of 18 report occasional alcohol use, and 10% report continued use during pregnancy (National Institute on Alcohol Abuse and Alcoholism, 2015). Bertrand et al. (2004) estimated rates of in utero alcohol exposure at 13% of all pregnancies with 3% of pregnant women reporting frequent (seven or more drinks per week) or binge drinking (five or more drinks in one setting). The prevalence of fetal alcohol syndrome in the USA is 0.3 per 1000 children between age 7 and 9 (Centers for Disease Control and Prevention (CDC), 2015b). Even very low levels of in utero exposure have been associated with adverse cognitive and other behavioral health effects, including inattention, reduced memory, hyperactivity, impulsivity, and aggression; these effects may persist into adolescence (Sokol, Delaney-Black, & Nordstrom, 2003; Sood et al., 2001). Alcohol exposure in the developing child can have equally devastating consequences. The creation of new brain cells during adolescence (and other times) is important for the development of optimal learning and memory capacity. Crews, Mdzinarishvili, Kim, He, and Nixon (2006) demonstrated that acute alcohol interfered with the formation of new neuronal cells in adolescent rats, a process that may disrupt optimal cognitive development. Structural changes have also been identified in adolescents and adults as a function of heavy alcohol consumption over many years. DeBellis et al. (2005) found reduced prefrontal cortex volume in adolescents with early onset alcohol use and comorbid mental health conditions, although the study design was not able to differentiate acquired from preexisting volume decrements. Another study by DeBellis et al. (2000) found reduced hippocampal volumes in individuals with early onset alcohol-use disorders, and age of onset was inversely associated with total volume, suggesting that hippocampal development and associated memory processes may be particularly vulnerable to the impairing effects of alcohol during adolescence. More recently, Treit et al. (2013) compared 5–15 year olds with Fetal Alcohol Spectrum Disorders (FASD) to age-matched controls in a longitudinal study capturing serial imaging and found delayed white matter development in frontal association tracts consistent with earlier MR and functional MR imaging studies (Ewing, Sakhardande, & Blakemore, 2014; Squeglia, Jacobus, & Tapert, 2014).

Adolescents using alcohol are at risk for cognitive impairments as a consequence of the toxic effects of alcohol on brain development. Brown and Tapert (2004) found visuospatial deficits and information retrieval deficits 3 weeks after adolescents detoxified from heavy drinking patterns. Among adolescents, the presence of an alcohol-use disorder has been associated with changes in working memory task performance (Sher, 2006). Changes such as these may contribute to a dynamic negatively spiraling interaction between biological and environmental risk factors. For example, students with low school connectedness are at increased risk of problematic use of alcohol, and if cognitive impairments develop with use, then the likeli-

hood of a negative trajectory of poor academic achievement and further disconnection with school is more likely, intensifying the risk for continued heavy alcohol use and dependence.

Environmental and biological factors may interact to influence risk. Exposure to traumatic experiences, such as violence, is a well-known risk factor for adolescent alcohol use (Vermeiren, Schwab-Stone, Deboutte, Leckman, & Ruchkin, 2003). Less dramatic, but not less important as a risk factor, the experience of stress in social interactions increases the risk for alcohol use and progression to dependence (Kreek & Koob, 1998). Animal models suggest that the effects of stress vary with age. For example, using a well-established place-preference conditioning procedure, Song et al. (2007) found that after exposure to chronic stress, adolescent mice demonstrated greater preference for an alcohol-paired environment, whereas for adult mice, the stress exposure did not change place preference.

Compared to adults, adolescent rats are less sensitive to sedation and motor impairment but more sensitive to social facilitation (Spear, 2004). Sensitivity differences have been associated with alcohol effects on NMDA receptor activity (Swartzwelder, Wilson, & Tayyeb, 1995). In humans, sensitivity to the effects of alcohol has been shown to be greater following fetal alcohol exposure and among individuals with a family history of alcohol dependence (Schuckit & Smith, 2004; Spear, 2002).

In addition to affecting the development of sensitivity and dependence, the age of initial alcohol use may also have an impact on response to treatment. Odansetron decreases alcohol craving by reducing serotonin receptor activity. Subjects with onset of alcohol dependence before the age of 25 years were found to have a more robust therapeutic response to odansetron than did those exhibiting alcohol-related problems at a later age (Johnson et al., 2000). An interesting study from Silveri (2014) using magnetic resonance spectroscopy to investigate the role of GABA in the comorbidity of impulse control, mental illness, and susceptibility to substance abuse found that a decreased GABA signal was associated with impulsivity among adolescents. This study provides a compelling rationale for considering non-benzodiazepine GABAergic medications, specifically topiramate, a well-known antiepileptic shown to be safe in the adolescent population, as a possible treatment medication (Silveri, 2014). By mimicking and replacing endogenous GABA at the level of cortex (the most likely site of antiepileptic activity), topiramate could be effective for treating adolescents prone to impulsivity and alcohol abuse.

Implications

There is a considerable body of evidence that the brain of the developing organism is at increased vulnerability to the adverse effects of alcohol from conception through adolescence, and that exposure to alcohol during this period of development may cause long-lasting or permanent neuroadaptation that may be associated with deficits in cognitive, emotional, and behavioral function during later life. These

findings underscore the critical importance of early prevention and treatment of alcohol problems among children and adolescents. Given growing evidence for the critical role of social context (e.g., traumatic experience, stress) in risk for alcohol use and abuse among adolescents, along with evidence that treatment interventions developed for adults may be less effective, it will be important moving forward to consider interventions for adolescents that address a broader range of factors than modulating the reinforcing effects of alcohol (e.g., acamprosate, naltrexone; Clark, 2012), particularly given that these treatment drugs may themselves have detrimental effects on the developing adolescent brain. Adolescents often exhibit a sense of invulnerability when evaluating risk (Cohn, Macfarlane, Yanez, & Imai, 1995), and impulsivity is closely linked with alcohol use among adolescents. Perhaps adopting more holistic approaches that include social interventions, psychotherapy, and increasing home stability that also target impulsivity will be as effective for managing alcohol problems with less developmental risk for adolescents (Simantov, Schoen, & Klein, 2000).

Marijuana

Marijuana is the most commonly used illicit substance among adolescents (Johnston et al., 2016). Following a rise in use that began during the 1960s, annual marijuana prevalence peaked among 12th graders in 1979 at 51%. From 1996 to 2016, past-month marijuana use was mostly steady among 8th (5.4%), 10th (14.0%), and 12th graders (22.5%). However, perception of harm is a strong predictor of future use and 68.9% of high school seniors do not view regular marijuana smoking as harmful. Because of this, along with increasing legalization and accessibility, there are concerns that rates may rise. Early observations suggest that states where marijuana has been decriminalized have reported a dramatic increase in poison control center calls and hospital admissions regarding pediatric marijuana ingestion (Wang et al., 2014).

Mechanisms of Action

Endocannabinoid receptors are found throughout the body with cannabinoid 1 (CB1) in the brain and cannabinoid 2 (CB2) in the immune system. The endogenous cannabinoid system impacts a range of bodily functions from appetite and sleep to memory and cognition and coordination. The main psychoactive chemical in marijuana is delta-9-tetrahydrocannabinol (THC), which binds to both the CB1 and CB2 receptors. Through its effects on cannabinoid receptors, THC interacts with an array of neurotransmitters and modulators including glutamate, GABA, and opioids (for a review see Martin, 2004). The dopaminergic pathway associated with reward systems is also modulated by endocannabinoid receptor activity.

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Marijuana Exposure

Marijuana use in pregnant adolescents and young adults is increasing at a greater rate than seen in older pregnant populations (Brown et al., 2017). Prenatal marijuana exposure has been associated with future developmental problems for the exposed fetus, including hyperactivity and lower attention span (Goldschmidt, Day, & Richardson, 2000) and difficulties with visual memory, analysis, and learning (Fried, O'Connell, & Watkinson, 1992; Fried & Watkinson, 2000; Goldschmidt et al., 2000; Pope & Yurgelun-Todd, 1996). Other difficulties include academic underachievement and increased risk of future marijuana and nicotine use (Day, Goldschmidt, & Thomas, 2006; Fergusson & Boden, 2008; Silins et al., 2014).

Beyond prenatal exposure, marijuana accumulates in breast milk, and the American Academy of Pediatrics (2013) believes breastfeeding is contraindicated in active marijuana users. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice (2015) recommends marijuana cessation prior to and during pregnancy.

Acute effects of marijuana use in adolescents can include mood instability, increased eating, decreased energy, and cognitive and psychomotor impairment (American Psychiatric Association, 2013). The user may experience euphoria, relaxation, heightened sensory perception and altered perception of time. Depending on the dose and the vulnerability of the user, hallucinations and panic can be experienced (National Institute on Drug Abuse (NIDA), 2017).

Several chronic health issues related to marijuana use are of concern, notably neurocognitive performance. Lane, Cherek, Tcheremissine, Steinberg, and Sharon (2007) have associated heavy use with poor performance on tasks requiring perseveration and decreases in flexible thinking and motivation. Other studies show a decrease in attention, learning, and memory (Harvey, Sellman, Porter, & Frampton, 2007; Solowij et al., 2011), and slower processing speed and verbal learning (Medina et al., 2007; Tapert, Granholm, Leedy, & Brown, 2002). Some studies suggest that when use begins before age 16 there is risk for a lower verbal IQ (Meier et al., 2012; Pope Jr., Gruber, Hudson, Huestis, & Yurgelun-Todd, 2003). That said, in prospective twin studies, Jackson et al. (2016) could not find a causal relationship between marijuana use and IQ loss but emphasized the potential importance of genetic and environmental factors.

In a review, Jacobus and Tapert (2014) highlight that in addition to the adverse performance on cognitive tasks, there may be changes in gray matter and neural functioning. Specifically, heavy use is associated with greater gray matter volume, particularly in the left hippocampal area that suggest interference with the normal developmental process of synaptic pruning of needless connections (Batalla et al., 2013; Medina et al., 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005). Beyond these specific observations of cognitive changes, there are general concerns about decline in social functioning, such as performance in school and on the job and interpersonal relations (McCaffrey, Pacula, Han, & Ellickson, 2010; National

Institute on Drug Abuse (NIDA), 2017). Other concerns include the association between heavy marijuana use and the development of psychosis, specifically schizophrenia in those with genetic vulnerabilities (Caspi et al., 2005; Gage, Munafò, MacLeod, Hickman, & Smith, 2015).

Whether these neurological, psychological, and behavioral changes are singularly related to the use of marijuana is not clear. There are questions of differences in the brains of young substance abusers before drug effects. Further complicating determination of causation is that pure use of only one substance is rare, making it difficult to determine which substance (tobacco, alcohol, marijuana or other drug use) has had the greatest impact on brain changes (Jacobus et al., 2016). Finally, in adolescents, marijuana is associated with other high risk activities, such as unprotected sexual behavior resulting in unplanned pregnancies and sexually transmitted diseases; motor vehicle accidents, including those with fatal outcomes; and other violent and accidental deaths (Brady & Li, 2014; Hartman & Huestis, 2013).

Implications

In their 2014 policy statement, the American Academy of Child and Adolescent Psychiatry (2014) summarizes the implications of marijuana use for children and adolescents as: "Marijuana use is not benign, and adolescents are especially vulnerable to its many known adverse effects (Jager & Ramsey, 2008; Schneider, 2008). One in six adolescent marijuana users develop cannabis use disorder, a well characterized syndrome involving tolerance, withdrawal, and continued use despite significant associated impairments (Anthony et al., 1994; Hasin et al., 2013). Heavy use during adolescence is associated with increased incidence and worsened course of psychotic, mood, anxiety, and substance use disorders across the lifespan (Hasin et al., 2013; Hayatbakhsh et al., 2007; Moore et al., 2007; Rubino, Zamberletti, & Parolaro, 2012). Furthermore, marijuana's deleterious effects on adolescent brain development, cognition, and social functioning may have immediate and long-term implications, including increased risk of motor vehicle accidents, sexual victimization, academic failure, lasting decline in intelligence measures, psychopathology, addiction, and psychosocial and occupational impairment (Champion et al., 2004; Fergusson & Boden, 2008; Fergusson, Horwood, & Swain-Campbell, 2002; Hall & Degenhardt, 2009; Hartman & Huestis, 2013; Lynskey & Hall, 2000; Meier et al., 2012; Shapiro & Buckley-Hunter, 2010)."

Opiates

An epidemic of illicit opioid use, evidenced by dramatic increases in opioid dependency, hospitalization and death, has emerged in recent years. During 2014, 47,055 deaths from overdose occurred in the US, more than any previous year on

record—61% of these deaths involved the use of opioids. Heroin related overdose deaths have more than tripled since 2010 (Rudd, Aleshire, Zibbell, & Matthew Gladden, 2016). Between 1997 and 2012, annual incidence of hospitalization for opioid poisoning among adolescents between ages 15 and 19 increased by 176%. Heroin poisoning showed an increase of 161% while methadone poisoning increased by 950% (Gaither, Leventhal, Ryan, & Camenga, 2016). Clearly, adolescent and young adult opioid use is emerging as a major public health concern.

Mechanisms of Action

Opioids belong to a chemical family of compounds that activate opioid receptors with differing affinities. The effects of these compounds on opioid receptors at different locations in the body produce the therapeutic effects of these drugs. Opium, derived from the Papaver somniverum, or poppy plant, has been used as an analgesic agent since at least 1500 BC Egypt. With minor chemical adjustments, opium can be made to permeate the blood brain barrier more effectively to calm the fussy infant, act more specifically at the level of the gastrointestinal system to reduce diarrhea, or target the pulmonary system as an antitussive. Opioid compounds that activate the μ-opioid receptor with different levels of affinity in the CNS, such as morphine, codeine, heroin, dihydromorphone, oxycodone, meperidine, fentanyl, methadone, and buprenorphine, contribute to the complex history of opiate abuse (Meyer & Quenzer, 2005).

The net result of increased opioid receptor binding is neuronal hyperpolarization which is accomplished in two main ways: (1) binding at inhibitory metabotropic G-protein coupled receptors, which decreases the activity of adenylate cyclase (AC) and open potassium channels, thereby hyperpolarizing postsynaptic cells, and (2) axo-axonically on other systems, decreasing the likelihood of calcium channel opening and, with it, the release of other families of target neurotransmitters, both excitatory and inhibitory. Of note, many endogenous neurons with opioid receptors also exhibit autoregulation, as presynaptic receptors are sensitive to the effects of endorphins. A slight variant on the opioid agonist theme is buprenorphine, which acts as a partial agonist at opioid receptors, regulating the magnitude of opioid receptor activation.

The density of opioid receptors varies across brain regions. Opioids are known for their ability to suppress respiratory drive by interfering with breathing pattern generation related to a high density of opioid receptors in the pons and medulla, making opioids among the most deadly drugs of abuse (Pattinson, 2008). As with almost all known drugs of abuse, molecular changes in dopamine function co-occur with opioid use during the process of addiction (Nestler, 2012), and such changes in dopamine function in the developing adolescent brain can have significant behavioral implications.

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Opioid Exposure

Various biopsychosocial factors have been implicated in illicit opioid use. Developmental vulnerability, stress, cultural permissiveness, substance use in the family or psychiatric illness can increase the risk of developing a substance use disorder (Sharma, Bruner, Barnett, & Fishman, 2016). Nonmedical prescription opioid users, for example, report greater psychological symptom burden compared to those that never use opioids (Boyd, Young, & McCabe, 2014). Increased availability of prescription opioids has also been identified as a factor contributing to the recent escalation of adolescent opioid abuse. Tormoehlen, Mowry, Bodle, and Rusyniak (2011) noted that increases in adolescent opioid abuse and associated medical complications increased following the 2000 Joint Commission on Accreditation of Healthcare Organizations (JCAHO) pain initiative, which highlighted importance of effective pain management for optimal health care. This initiative had a major influence on clinical practice for pain management and promoted more liberal use of opioid prescriptions, which in turn escalated the volume of prescription opioid medication being dispensed to the general population. Greater access to nonmedical prescription opioids via diversion from friends and relatives was reported by 12th graders participating in the Monitoring the Future (MTF) drug-use survey (Johnston et al., 2016). Indications of nonmedical use of prescription drugs have been detected in 2.3 of 11 million tweets on the popular Twitter platform, reflecting the potential impact of social media on drug-use behavior (Kalyanam, Katsuki, Lanckriet, & Mackey, 2017).

The highest rate of heroin use occurs between 18 and 25 years of age, with use of nonmedical prescription opioids being a strong predictor of future heroin use among adolescents, especially among those who first use between the ages of 10 and 12 (Cerdá, Santaella, Marshall, Kim, & Martins, 2015). Data from the MTF study indicate that the rate of intravenous heroin use remains low at 0.3% among high school seniors, while the rate of nonmedical prescription opioid use has been decreasing over the past 4 years (Johnston et al., 2016). Though promising, adolescents continue to be at risk for early transition to heroin. Onset of opioid use during adolescence is associated with shorter duration from first use to dependence (Clark, Kirisci, & Tarter, 1998). Early initiation of heroin use is associated with a number of adverse life events, including a greater likelihood of dropping out of school, using/sharing needles, criminal behavior and meeting diagnostic criteria for an opioid use disorder. Health risks associated with needle use include Hepatitis C and HIV (Subramaniam, Fishman, & Woody, 2009; Subramaniam & Stitzer, 2009).

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome (NAS) describes a constellation of findings displayed by a newborn as a result of abrupt withdrawal from exposure to opioids due to maternal use. Substantial increases in NAS have occurred over the last decade. Following a threefold increase between 2000 and 2009, incidence continued to rise from 3.4 to 5.8 per 1000 births between 2009 and 2012. In 2012, 21,732 infants were diagnosed in the USA (Patrick, Davis, Lehman, & Cooper, 2015). First described by Dr. Loretta Finnegan in the 1970s, the syndrome is still poorly understood with factors of licit/illicit substance exposure, genetic predisposition and epigenetic modifications that, along with maternal physiology, can lead to significant morbidity (Jansson & Velez, 2012). Manifestation of NAS can be grouped into metabolic findings, such as fever and sweating, gastrointestinal (vomiting, loose watery stools) and central nervous system findings such as tremors, seizures, and increased muscle tone (McQueen & Murphy-Oikonen, 2016). Though an NAS can be produced from a variety of chemical offenders, its association with opioid exposure is common and requires early detection. Urine or meconium drug screens can assist in detecting opioids along with other substances associated with increased severity, such as benzodiazepines. Clinical observation, along with use of severity tools like the Finnegan scoring system, can direct treatment with nonpharmaceutical intervention as the preferable first option. Mothers who have been treated with methadone or buprenorphine as part of medication-assisted treatment can breastfeed, which has shown to reduce the need for pharmaceutical intervention and length of stay in the hospital (Kocherlakota, 2014).

Health consequences of NAS are significant. In the words of Anand and Campbell-Yeo (2015), “After adjusting for confounders, illicit opioid abuse was associated with increased odds of preterm labor, early onset delivery, poor fetal growth, prematurity and stillbirth... Another study found increased odds of maternal death (4.6-fold), cardiac arrest (3.6-fold), intrauterine growth restriction (2.7-fold), placental abruption (2.4-fold), preterm labor (2.1-fold), oligohydramnios (1.7-fold), stillbirth (1.5-fold) and premature rupture of membranes (1.4-fold) associated with illicit opioid abuse. Preterm birth occurred three times more commonly in primiparous mothers hospitalized for opioid abuse (other drugs), and their babies were six times more likely to require NICU admission.”

An interaction of genes for opioid drug transport through the placenta, maternal metabolism, and fetal metabolism make NAS a highly variable phenomenon, difficult to predict based on amount or type of opiate ingested during pregnancy, alone. In a large cohort study of Medicaid patients who were pregnant, 23% filled an opiate prescription at some point during their pregnancy (Desai, Hernandez-Diaz, Bateman, & Huybrechts, 2014), suggesting that risk for NAS may occur in as many as one in every four patients. Recent studies have demonstrated that methadone is able to induce the synthesis of opiate transporters in the placenta, thereby increasing fetal exposure to opioid drugs. Because the factors impacting the development of NAS remain obscure, any opioid use during pregnancy should be identified as a potential health risk.

Although the exact mechanism and frequency remains unclear, opioid exposure in utero has been associated with changes in timing of myelination, dendritic growth changes, cortical pyramidal neuron growth and migration, basal ganglia volume, and lifelong behavioral changes including hyperactivity, inattention, ADHD symptoms, and impulsivity (Anand & Campbell-Yeo, 2015; Fodor, Tímár, & Zelena, 2014). In this manner, opioid addicted mothers, who often have had difficulty receiving prenatal care due to their addiction, bring children who as a result of prenatal opioid exposure are predisposed to impulsive decision-making, into an unstable home environment wherein opiates are ubiquitously available, thereby promoting an escalating cycle of opioid-related adverse health outcomes.

Implications

Across the lifespan, illicit opioid use can have a devastating impact on the neurodevelopment of a growing child. In utero exposure to opioids can lead to fetal distress and various pregnancy or birth complications. There is currently controversy over the use of medication-assisted treatment (MAT) in opioid dependent pregnant women. A meta-analysis comparing buprenorphine to methadone, both evidenced based treatments for opioid dependence, noted lower risk of preterm birth with improved birth weight and head circumference among mothers treated with buprenorphine (Zedler et al., 2016). In turn, buprenorphine has been shown to be superior to methadone in the treatment of NAS (Hall et al., 2016). Progressing through childhood, availability of opioids in the household continues to pose a risk. According to one study using data from 1996 to 2012, opioid prescriptions to children and adolescents remained low, 2.68% and 2.91%, respectively. In contrast, opioid prescriptions to family members increased during this time (Groenewald, Rabbitts, Gebert, & Palermo, 2016). Children and adolescents are being exposed to nonmedical prescription opioid through friends and family, putting them at risk of dependence or transition to heroin use. Gaither et al. (2016) observed that the largest increase in hospitalization for opioid poisoning was among 1- to 4-year-old children. The study further commented that opioid poisoning in children older than 10 were primarily associated with suicide attempts. Continued efforts in limiting access to opioids through improved prescribing practices and diversion are a priority. In addition, recognition of risk factors such as poverty, genetic predisposition, and ADHD, has received attention in the literature, as has the use of medication-assisted treatment, which has garnered support among pediatricians (Ryan et al., 2016).

Therapeutic Stimulants

Stimulants are the most frequently prescribed and thoroughly investigated medications for the management of ADHD (e.g., Barkley, 1991; Swanson et al., 2002; Zito et al., 1999), which is most commonly diagnosed and treated during childhood.

Medical use of stimulants has steadily increased in the past 20 years, and use in the USA is much greater than in other countries (Scheffler, Hinshaw, Modrek, & Levine, 2007; Zuvekas, Vitiello, & Norquist, 2006). In 2011, it was estimated that 6.1% of children 4–17 years of age were currently taking medication for ADHD in the USA (Visser et al., 2014). Associated with the rise in therapeutic stimulant use, there is increasing concern about the misuse of stimulants by students and the diversion of prescription stimulants both in college student and patient populations (McCabe, Teter, & Boyd, 2004, 2006a, 2006b; McCabe, Teter, Boyd, & Guthrie, 2004; Upadhyaya et al., 2005; Wilens, Gignac, Swezey, Monuteaux, & Biederman, 2006). Commensurate with this rise in use, emergency department visits associated with nonmedical use of prescription stimulants in the USA have been steadily increasing, with approximately 5000 visits occurring in 2004, increasing to approximately 22,000 visits in 2011 (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013b).

Mechanisms of Action

Most therapeutic stimulants have two overlapping neuropharmacological effects: they inhibit monoamine reuptake and they enhance monoamine neurotransmitter release. Both these actions increase the extracellular concentrations of dopamine and norepinephrine, although magnitude of effect is greater at dopamine sites, particularly those in the dopamine reward pathway (e.g., Solanto, 1998; Volkow et al., 2001). The specific mechanisms by which these effects are produced vary among the different stimulant medications (e.g., Ritalin, Adderall, and Dexedrine). Increased extracellular dopamine and norepinephrine is associated with enhanced wakefulness, alertness, mood, initiative, confidence, concentration, motor activity, and task performance and decreased fatigue.

Epidemiology and Health Consequences of Prenatal, Early Childhood, and Adolescent Stimulant Exposure

While it had long been thought that abuse of prescription stimulant medication was low, recent evidence suggests that prescription stimulant misuse may be a growing problem. In healthy adults, stimulant medications function as potent reinforcers and have a well-established abuse liability (e.g., Henningfield, Johnson, Jasinski, & Bozarth, 1987; Jasinski, Johnson, & Henningfield, 1984; Martin, Sloan, Sapira, & Jasinski, 1971). Nonmedical prescription stimulant use (i.e., diversion of prescription medication) appears to be on the rise. For example, one study found that 61.7% of college students had diverted their ADHD medication at least once (Garnier et al., 2010). Significant numbers of college-aged individuals who have received

prescriptions for stimulant medication report misusing their own or other prescription medication (Arria et al., 2008; Upadhyaya, Rose, et al., 2005). Many of those who misuse prescription medication meet the criteria for conduct disorder and substance use disorder (Wilens et al., 2006). Diversion of prescription stimulant medication in college-aged students who initiated treatment in grade school is no greater than that of the general population, but diversion escalates among college-aged students who were first prescribed stimulant medication after completing grade school (McCabe et al., 2006a).

Nonmedical stimulant use is prevalent among adolescents. Poulin (2007) reported that about 26% of junior and senior high school students who were receiving prescribed stimulants had given or sold their medication to others, though another sample including middle- and high-school students found only a 10% diversion rate (Epstein-Ngo et al., 2016). Illicit stimulant medication use among high school students has been linked with the use of other drugs, including tobacco cigarette smoking, heavy episodic drinking, marijuana and cocaine use (McCabe, Boyd, & Teter, 2009; McCabe, Teter, & Boyd, 2004; Poulin, 2007).

While there is risk for the misuse of prescription stimulants, these medications may be protective for other forms of drug abuse. Individuals with ADHD are at a higher risk for developing a substance use problem (Lee, Humphreys, Flory, Liu, & Glass, 2011). Some research, however, has suggested that treatment of ADHD with stimulant medications reduces the risk for substance use disorders (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2014; Wilens et al., 2008). A recent meta-analysis (Humphreys, Eng, & Lee, 2013) and a topical review (Zulauf, Sprich, Safren, & Wilens, 2014), however, both suggest that treatment of ADHD with a stimulant medication is neither protective nor a risk factor for the development of a substance abuse problem. Due to a lack of consensus on this topic, more research is required to determine what the effect of stimulant medications is on the development of substance use problems among individuals being treated for ADHD.

A recent report found a significant increase in the use of stimulant medications among pregnant women between 1998 (0.2%) and 2013 (1.3%) (Louik, Kerr, Kelley, & Mitchell, 2015). While research on prenatal exposure to stimulant medications in humans is scarce, several studies examining the potential teratogenic effects of nonmedical stimulant use (cocaine and methamphetamine) have been conducted and found growth restrictive effects on the fetus (Bada et al., 2002; Smith et al., 2006). Preclinical studies on stimulant medications indicate that exposure to these drugs during early brain development can cause lasting effects at the cellular level. For example, daily prenatal exposure to dl-amphetamine (0.5 mg/kg/day) induced changes in the biochemistry of the central catecholaminergic system of the adult rat (Nasello, Astrada, & Ramirez, 1974; Nasello & Ramirez, 1978a, 1978b; Ramirez & Carrer, 1983; Ramirez, Carrer, & Nasello, 1979). Nasif, Cuadra, and Ramirez (1999) did not observe any gross teratogenic effects of prenatal exposure to d-amphetamine, but did observe decreased firing rate of norepinephrine neurons in the locus ceruleus in adult rats that had received prenatal exposure to the drug. This preclinical evidence suggests that prenatal exposure to stimulant drugs might produce long-term changes in neuronal cellular function in humans. Consistent with

this research, the Food and Drug Administration (FDA) has placed therapeutic stimulants in Category C (i.e., animal reproduction studies have shown an adverse effect on the fetus, or there are no adequate and well-controlled studies in humans, and/or the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks), and as such, these medications should be prescribed to pregnant women only if the benefit justifies the potential risk to the fetus (Berkowitz, Coustan, & Mochizuki, 1998).

Preclinical studies suggest that exposure to stimulant medication during early childhood may have the potential to disrupt the normal sequence of gene expression in the developing brain, resulting in altered neurochemistry and behavior, and that these effects can endure into adulthood (Chase, Carrey, Brown, & Wilkinson, 2005a). Moll, Hause, Ruether, Rothenberger, and Huether (2001), for example, found that methylphenidate exposure in young rats caused a 25% decrease in the density of striatal dopamine transporters, which persisted into adulthood, even after discontinuation of the medication in the prepubertal rat. In a three-part study using adolescent gerbils, Grund et al. (2007) demonstrated that (1) early exposure to methamphetamine resulted in a 30% decrease in dopamine fiber innervations in the prefrontal cortex and amygdala complex; (2) these abnormalities were prevented by methylphenidate administration during adolescence; and (3) methylphenidate alone did not alter dopamine innervation. Researchers have also documented other effects of stimulant medications on gene expression, but the clinical implications remain to be explored (Chase, Carrey, Brown, & Wilkinson, 2005b; Chase, Carrey, Soo, & Wilkinson, 2007; Hawken, Brown, Carrey, & Wilkinson, 2004). Preclinical evidence, however, demonstrates that adolescent exposure to methylphenidate causes persistent neurobehavioral consequences including decreased sensitivity to natural and drug rewards, and long-term modulation of self-control (Adriani, Zoratto, & Laviola, 2011; Marco et al., 2011). Further research is required to determine if these effects are present in humans.

Sensitization (progressively augmented behavioral response following repetitive administration of a drug) and cross-sensitization associated with repeated or chronic stimulant administration have been commonly reported in preclinical studies (Brandon, Marinelli, Baker, & White, 2001; Gaytan, Yang, Swann, & Dafny, 2000; Guerriero, Hayes, Dhaliwal, Ren, & Kosofsky, 2006; Kuczenski & Segal, 2001, 2002; Marco et al., 2011; Torres-Reveron & Dow-Edwards, 2005; Yang, Swann, & Dafny, 2003). Valvassori et al. (2007) demonstrated that early exposure to methylphenidate in adolescent rats resulted in augmented locomotor response after amphetamine challenge as compared to controls, suggesting pretreatment with methylphenidate during adolescence elicited cross-sensitization (the behavioral augmentation that occurs when pretreatment leads to a greater sensitivity to another substance). Methylphenidate and amphetamine have also been shown to increase nicotine administration in rats, suggesting that methylphenidate and amphetamine might engender increased sensitization to the reinforcing effects of nicotine (Santos, Marin, Cruz, DeLucia, & Planeta, 2009; Wooters, Neugebauer, Rush, & Bardo, 2008). Clinical research has, however, failed to find increased rates of tobacco use among adolescents treated with methylphenidate (e.g., Hammerness et al., 2013).

Among children, the most common side effects of therapeutic stimulant use are insomnia, decreased appetite and weight loss, headache, fatigue, abdominal cramps, jitteriness, increase in heart rate and blood pressure, and emotional liability including depression, irritability, and increased frequency of crying. Delirium, psychotic symptoms with vivid hallucinations, and paranoia can be seen with higher doses. Stimulants have peripheral adrenergic effects and increase systolic and diastolic blood pressure and heart rate (Efron, Jarman, & Barker, 1998; Harvanko, Martin, Lile, Kryscio, & Kelly, 2016; Wolraich & Doffing, 2004). Amphetamine abuse is associated with increased risk of hemorrhagic stroke in young adults (Westover, McBride, & Haley, 2007). (Note: FDA requires a warning label on stimulant drugs used to treat ADHD because stimulants cause a rise in blood pressure and heart rate and may increase the risk of heart attack, stroke, or sudden death (Charatan, 2006).)

As mentioned earlier, stimulant medications have a well-documented abuse liability among healthy adults. There is also evidence suggesting that stimulant medications may have abuse liability in children and adolescents. In 1937, Bradley demonstrated that hospitalized children reported positive subjective effects, such as euphoria, following the administration of Benzedrine. Martin, Guenther, Bingcang, Rayens, and Kelly (2007) examined the behavioral effects of methylphenidate (0, 0.25 mg/kg) under randomized, double-blind conditions in 24 children with ADHD between the ages of 11 and 15 years. Methylphenidate increased measures of abuse liability adopted for use in children with ADHD (e.g., modified MBG scale of the Addiction Research Center Inventory). In a pilot study, Fredericks and Kollins (2005) observed that three of the five children and adolescents with ADHD reliably chose methylphenidate over placebo under controlled double-blind conditions, suggesting that the drug functions as a reinforcer under some conditions. In an earlier study, they found that young adults with ADHD chose methylphenidate significantly more frequently than placebo or no capsule (Fredericks & Kollins, 2004). The subjects who chose methylphenidate more reliably exhibited greater methylphenidate-induced reductions in ADHD symptoms, suggesting that the reinforcing effects of the drug may be associated with the drug's therapeutic effect. These results suggest that stimulant medications may have abuse liability in children comparable to that in adults. However, it is important to note that even given these concerns, if used as prescribed, stimulants have a high margin of safety and have been used effectively for decades in treating ADHD (Barkley, 1991; Klein-Schwartz, 2002; Swanson et al., 2002; Weyandt et al., 2014; Zito et al., 1999).

Implications

It is essential that stimulants should be prescribed only for well-documented disorders. For example, if an adolescent presents for the first time with symptoms of ADHD, the diagnosis must be made rigorously with input from the adolescent, as well as confirmation from parents and educators. Standardized and structured testing, including the Conners Rating Scale, can assist in validation of the diagnosis

(Conners, Sitarenios, Parker, & Epstein, 1998). The Achenbach, Connors, Quay behavior (ACQ) check list for parents, teachers, and youth is also useful for confirming the diagnosis of ADHD and can be used to evaluate comorbidities such as conduct disorder (Achenbach, 1991). Self-report measures and urine drug screening may be helpful in assessing whether or not the patient has a comorbid substance use disorder.

In the clinical setting the decision to use stimulants to treat ADHD may be especially challenging for parents when their adolescents are at the age when risk for experimentation with drugs is increasing. Parents are often concerned about whether the medical use of stimulants could increase the risk of future drug use in their children. The medical and scientific community has also raised concerns about ongoing psychostimulant treatment based on compelling preclinical evidence for the development and persistence of behavioral consequences following repeated exposure to psychostimulants, particularly among adolescent animals (for review see Marco et al., 2011), as well as growing numbers of reports of misuse and diversion of prescription stimulants (Benson, Flory, Humphreys, & Lee, 2015; Poulin, 2007; Upadhyaya, Deas, & Brady, 2005a; Wilens et al., 2006). Clinicians who prescribe stimulants (pediatricians, child psychiatrists, family physicians, and neurologists) should inform their patients of the risk of medication diversion. Patients and, if appropriate, their parents should be informed of potential pressures to share or sell stimulant medication. Prescription-monitoring programs should be considered (Sussman, Pentz, Spruijt-Metz, & Miller, 2006), and random urine drug screening could aid in early identification and prevention of prescription misuse and diversion. Likewise, adolescents who are not being treated for ADHD should be warned about the risks of nonmedical use of prescription medication.

Prescription stimulant misuse and diversion is more likely among individuals with ADHD who are not diagnosed or treated until entering high school. Late treatment and undertreatment of ADHD is associated with the emergence of a constellation of high-risk behaviors; drug diversion may be an element of this constellation. It is equally possible that ADHD is not easily diagnosed in some individuals until supplemental symptom clusters or associated comorbidities, such as sensation seeking or conduct disorder, emerge during the developmental process (Martin et al., 2004). It may be that this subgroup of ADHD adolescents who are engaged in a range of problem behaviors, including other drug use and poor school performance, are at increased risk for misuse and diversion of prescription stimulants (McCabe, Teter, & Boyd, 2004; McCabe, Teter, Boyd, & Guthrie, 2004). While stimulants are the first-line treatment for early-onset ADHD, it remains to be seen whether they should be used for late-onset ADHD patients with high-risk behavioral comorbidities. Interestingly, Klein et al. (1997) demonstrated that high-dose stimulants enhanced outcome of ADHD with comorbid conduct disorder, and Biederman, Wilens, Mick, Spencer, and Faraone (1999) observed that drug use did not escalate when ADHD adolescents and young adults with substance abuse disorders were treated with stimulants.

Conclusions

This chapter examines the neurobiological implications of exposure to caffeine, nicotine, alcohol, marijuana, opiates, and therapeutic stimulants, the drugs of abuse that are most frequently encountered during human development. Each of these drugs produces potent neuropharmacological effects on brain function. While it remains difficult to isolate direct causal influences and disentangle the direct effects of drug exposure from indirect effects associated with environmental, social, and cultural influences that are often closely associated with drug exposure, particularly in clinical studies, this chapter provides compelling evidence that developmental exposure to drugs of abuse can have both subtle and dramatic effects with important behavioral and societal consequences. Levels of exposure are substantial during all phases of development (i.e., prenatal, postnatal, childhood, and adolescence), and evidence indicates that exposure to these drugs during critical phases of development have both short-term and long-term consequences. Of critical importance, exposure to psychoactive drugs of abuse during critical periods of development can engender increased sensitivity to the neuropharmacological effects of drugs, which, in turn, leads to increased frequencies of drug use and further changes in sensitivity (e.g., Derauf et al., 2009; Glantz & Chambers, 2006).

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