

Review

Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring

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Abstract

Teratological investigations have demonstrated that agents that are relatively harmless to the mother may have significant negative consequences to the fetus. Among these agents, prenatal alcohol, nicotine or cannabis exposure have been related to adverse offspring outcomes. Although there is a relatively extensive body of literature that has focused upon birth and behavioral outcomes in newborns and infants after prenatal exposure to maternal smoking, drinking and, to a lesser extent, cannabis use, information on neurobehavioral and cognitive teratogenic findings beyond these early ages is still quite limited. Furthermore, most studies have focused on prenatal exposure to heavy levels of smoking, drinking or cannabis use. Few recent studies have paid attention to low or moderate levels of exposure to these substances. This review endeavors to provide an overview of such studies, and includes animal findings and potential mechanisms that may explain the mostly subtle effects found on neurobehavioral and cognitive outcomes. It is concluded that prenatal exposure to either maternal smoking, alcohol or cannabis use is related to some common neurobehavioral and cognitive outcomes, including symptoms of ADHD (inattention, impulsivity), increased externalizing behavior, decreased general cognitive functioning, and deficits in learning and memory tasks.

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1. Background and theoretical framework

Studies of behavioral and cognitive effects of in-pregnancy exposures, such as stress and undernutrition, often treat prenatal substance use as a confounding variable without addressing the role of these lifestyle factors, such as smoking, drinking, or cannabis use, on the offspring as a direct or interactive agent. However, drug abuse during pregnancy has also been related to postnatal consequences, manifested as alterations in behavior and cognition.

Research into these mostly subtle associations between prenatal smoking, drinking or cannabis use and offspring outcome utilizes the concepts and methods of behavioral teratology (Vorhees, 1989). The identification of the fetal alcohol syndrome (FAS) in the 1970s was an important milestone in bringing the value of the behavioral teratological approach to human studies. Since the description of FAS, there has been a dramatic increase in the number of research reports examining the neurobehavioral and cognitive consequences in young babies who have been exposed to a myriad of drugs during prenatal development (Fried, 2002).

Over the years, teratological investigators have demonstrated that agents that are relatively harmless to the mother may have significant negative consequences to the fetus (Annau and Eccles, 1986). Vorhees (1989) has modified and extended general teratological principles to research in behavioral teratology, resulting in two major postulates (Fried, 1998): (1) vulnerability of the central nervous system (CNS) to injury extends throughout the fetal, neonatal periods and beyond the infancy stage, including all aspects of nervous system development (e.g. neurogenesis, neuronal differentiation, arborization, synaptogenesis, functional synaptic organization, myelination, gliogenesis, glial migration and differentiation), and (2) the most frequent manifestation of injury to the developing CNS does not result in nervous system malformations but rather in functional abnormalities that may not be detectable at birth.

Substances that are most frequently used by pregnant women include nicotine, alcohol, and cannabis. Although there is a relatively extensive body of literature that has focused upon birth and behavioral outcomes in newborns and infants after prenatal exposure to maternal smoking, drinking and, to a lesser extent, cannabis use, information on

neurobehavioral and cognitive teratogenic findings beyond these early ages is still quite limited. Furthermore, most studies have focused on prenatal exposure to heavy levels of smoking, drinking or cannabis use, whereas only few recent studies have paid attention to low or moderate levels of exposure to these substances. This review summarizes the studies that have addressed the possible association of low to moderate levels of maternal smoking, drinking or cannabis use during pregnancy with neurobehavioral and cognitive outcomes in the human offspring. This review aims to examine (1) whether in particular low to moderate prenatal exposure to maternal smoking, drinking or cannabis use results in common or specific neurobehavioral and cognitive outcomes in the human offspring, and (2) which mechanisms may account for the relationship between prenatal substance exposure and neurobehavioral and cognitive outcomes in offspring. To address the second aim, some findings from animal studies are included as well, because they may increase our insight into the possible mechanisms underlying the potential harmful effects of maternal smoking, drinking or cannabis use during pregnancy on later offspring behavior and cognition. Furthermore, the use of animal models permits control of environmental factors, which may become critical to validate findings in humans. However, when generalizing the results of animal models to humans there are some caveats. For instance, the species differ in the timing of brain maturation. It is important to scale developmental processes in animals to those in humans, and it is particularly important to take into account differences in the stage of brain development at the time of birth (Huizink et al., 2004). Besides, species differences in vulnerability to substances can exist (Goodlett and Horn, 2001).

2. Perturbations in neurodevelopment

During fetal development, every area, system, and circuit of the brain has its growth spurts. If the area does not fully develop in those assigned periods, the developing brain does not compensate; the area is left with a deficit. Genetic expression moves on to develop the next scheduled area (Watson et al., 1999). Thus, the timing of the perturbation in neurodevelopment may be critical in determining if a neurobehavioral or cognitive deficit results, and the timing

of the disruption in neurodevelopment may also determine the type of deficit that results (Watson et al., 1999). The enduring impact of an early insult depends on the maturational stage of exposure such that perturbations in the synaptic milieu redirect the normal developmental trajectory (Andersen, 2003). The growth of the central nervous system is a process that continues postnatally. Therefore, the evaluation of particular dysfunctions after prenatal substance exposure may not be possible until the child is older (Fried, 2002).

Unfortunately, only very few human studies have been able to focus on prenatal exposure to substances within a certain period of pregnancy to determine critical time windows with regard to perturbations in neurodevelopment. This is due to the fact that most pregnant women who smoke, drink or use cannabis will either discontinue this habit during or after the first part of pregnancy (after recognition of their pregnancy) or continue using throughout pregnancy (Coleman, 2004; Richardson et al., 1995). Therefore, exposure during, for instance, the second trimester only is very unlikely to occur. Moreover, many studies have used retrospective designs in which it is rather difficult to obtain valid information on the exact timing of prenatal exposure to substances. Thus, due to this lack of information, this review focuses on prenatal exposure to substances without paying attention to the specific timing of exposure.

3. Methodological issues

Several methodological aspects should be considered when reviewing human studies on the association of prenatal maternal teratogenic factors and child and adolescent neurobehavioral and cognitive outcomes.

3.1. Study design

Most studies have been performed retrospectively. Even in most studies that have longitudinal designs, in which the offspring is followed up for many years, the prenatal exposure measure was assessed after birth. One problem related to self-reported substance use during pregnancy in these studies is the likelihood of recall bias. Another problem concerns possible differential misclassification.

When investigating the longer-term consequences of prenatal exposure to nicotine, alcohol or cannabis, a longitudinal, follow-up, prospective design allows the researcher to observe the child in a systematic manner and recall bias with regard to nicotine, alcohol or cannabis is minimized. Moreover, a prospective design has the opportunity to determine the extent and timing of drug exposure during pregnancy, to include a biochemical verification of the self-report on substance use, and to evaluate more accurately the covariates. In these studies,

women are recruited during pregnancy and their offspring is then followed for a long period.

Alternative approaches are cross-sectional designs, in which children are assessed at a particular developmental stage or age. These cross-sectional designs have been mostly set-up as case-control studies, in which highly exposed subjects are compared to non-exposed controls. In various studies using a case-control design, clinic-referred samples are used as 'cases'. In fact, several studies on prenatal substance exposure and infant outcomes have been performed in clinical populations. Within these populations, it is likely that other factors, such as maternal and fetal malnutrition, lack of adequate prenatal medical care, exposure to sexually transmitted and other infectious diseases, polydrug use, impoverished housing, or postnatal parental drug abuse may confound the relationship (Malanga and Kosofsky, 2003). Moreover, these samples may be affected by selection bias, because clinical samples are not usually a true and representative sample of cases, but rather tend to be the more complex ones, with for instance more comorbidity. This is referred to as Berkson's bias (Berkson, 1946). For example, FAS children who are also hyperactive are more likely to be referred for treatment because their behavior is disruptive in family and school settings.

Although these cross-sectional and case-control research designs have offered the basic knowledge on consequences of prenatal substance exposure, and are less time and money consuming, the prospective longitudinal designs are methodologically to be preferred.

3.2. Measurement of exposure variables

Results of studies should be judged on the accuracy with which the exposure variables are measured.

Information bias with regard to the actual exposure is a threat to the validity of the results. One source of information bias is related to the self-report of substance use in pregnancy. Since humans use substances voluntarily, there is no experimental control over the dose administered or the pattern of use. It is possible that pregnant women may underreport their actual use of substances. Thus, it is difficult to obtain a reliable and valid measure of prenatal substance use. However, some researchers have suggested that retrospective reporting of substance use during pregnancy may obtain more valid measures, because women may underreport levels if asked during pregnancy because of stigma associated with substance use at that time. Especially, when pregnancy has passed and there is no discernible major adverse effect on the child, the mother may be forthright in her reporting (Ernhardt et al., 1988; Jacobson et al., 1991). In contrast, others have shown that a detailed interview procedure during pregnancy provides a more accurate and reliable assessment than retrospective recall (e.g. Jacobson and Jacobson, 2002).

Another aspect concerns the classification of exposure measures. Dichotomization of exposure may hide a true association, and may limit the detection of a possible dose–response effect. Averaging substance exposure over the total period of pregnancy, which has been done in several studies, could obscure the fact that there may be important subgroups of women who use a substance more heavily in one period of pregnancy. For example, women who are binge drinkers may drink a lot at a few occasions during the first period of pregnancy and may not use alcohol in the later trimesters.

A solution to these methodological problems is a direct measurement of substance and their metabolites exposure at regular intervals during pregnancy. Direct measurement may also be useful to validate the self-reported measures of exposure.

3.3. Outcome measures

It is of importance to realize that measurements during the very early life of the offspring may provide a picture of the immediate status of the young infant, but are of limited value in identifying enduring outcomes within neurobehavioral and cognitive domains. In addition, drug exposure in utero may produce transitory effects. Another issue with regard to outcome measures reflects the topic of (in) stability of performance from infancy to childhood and adolescence. It is likely that the effect of teratogens will not be constant across ages (Fried, 2002). In addition, it may be difficult to obtain a reliable assessment of child behavior and development based on maternal report. Furthermore, some behaviors of interest are not testable in the neurologically still immature baby and these effects may manifest themselves only when that portion of the CNS underlying the behavior in question is sufficiently developed (Fried, 2002). An example is executive functioning, which reflects prefrontal brain functioning, and which does not reach full maturity until puberty. Also, later substance (ab)use of prenatally exposed offspring can only be determined at later ages. Therefore, long-term follow-up studies are needed to assess these outcomes. However, such long-term follow-up studies require a lot of time and investment, in particular to reduce the possibility of selective drop-outs.

Finally, when reviewing studies on prenatal substance exposure, it should be noticed that the choice of outcome measures, and the method of assessment vary between studies. Therefore, the results are not always comparable.

3.4. Statistical issues

Statistical power of many studies may be limited. A large study cohort is especially needed when outcome is rare or the effect is small. Moreover, it is sometimes impossible to identify the main determinant that predicts the outcome of interest, because in human studies various exposure

variables (e.g. smoking and alcohol use) are often correlated. To test the separate effects of these exposures, a rather large total sample size is needed, in which large enough subgroups exposed to only one substance can be formed, and preferably, compared to a subgroup of polydrug users as well. For such a design, population-based large cohorts are needed, with enough variation in substance use during pregnancy.

Another issue concerns the extent to which statistical associations between maternal substance use during pregnancy and later adjustment reflect cause-and-effect associations or non-causal, or spurious, associations that arise because of the social background, behavioral characteristics, and child-rearing practices of mothers who elect to use substances such as nicotine, alcohol or cannabis during pregnancy. A range of environmental factors may also account for deficits in behavior or cognition of infants. For instance, negative alterations in nutritional status, lower social background, and more problematic parental and family functioning, associated with maternal substance use during pregnancy, could lead to spurious correlations between maternal substance use during pregnancy and neurobehavioral and cognitive outcomes in offspring (Fergusson et al., 1998; Lynch et al., 2003; Haynes et al., 2003). Also, psychological factors may account for neurobehavioral and cognitive outcomes. For instance, Cornelius et al. (2001) found that heavy and moderate smokers received less prenatal care, recognized their pregnancies later, and reported more symptoms of depression than did non-smokers and light smokers. Furthermore, the environment in which the child is raised may well be unpredictable and unstable when their mothers are alcohol abusers (O'Connor et al., 2002a). These factors may hamper mother–child interactions, which in turn may affect child neurodevelopment. Thus, in determining the possible influence of the environment during the development of the child, social, psychological and demographic factors must be considered. Therefore, taking these covariates into account is essential. In short, among the covariates are: (1) family characteristics, such as social and ethnic background, psychiatric history of both parents, including parental substance use, parenting style, family functioning, and maternal age, (2) substance use characteristics, such as exposure to a variety of substances, intensity and timing of consumption, and (3) child characteristics, such as birth outcome (birth weight, gestational age at birth), parity, and sex.

A related issue is the likelihood that women who used substances during pregnancy will continue doing so after the birth of the child. Also, postnatal passive smoking effects have been found on the behavior and development of the infant. For offspring of mothers who use substances such as nicotine and alcohol and breast-feed, substance levels could constitute a significant source of environmental exposure (Buka et al., 2003).

3.5. Interpretation of results

Some studies speak of causal relationships whereas others speak of associations when discussing their results with regard to prenatal substance exposure and offspring outcome. For causal relationships between prenatal exposure to substances and later behavioral or cognitive outcomes, evidence should accumulate along five domains: biologic plausibility, consistency, temporality, dose–response gradient, and strength of association (e.g. Rothman and Greenland, 1998). Most of the biologic plausibility is rooted in the strength of animal research. The temporal sequence of exposure coming prior to outcome is also clearly evident in animal models, in which also dose–response relationships have been found. This pattern of association is a strong argument in favour of an effect of prenatal substance exposure. The strength of the association between prenatal exposure to a substance and child outcome is an important consideration, because strong associations are unlikely to be explained away by other factors (Weitzman et al., 2002). However, the sample size of the study needs to be considered. Because the standard error is related to sample size, a small group of participants may fail to detect a difference.

The expected effects of (moderate) prenatal substance exposure on neurobehavioral and cognitive outcomes are not large. Therefore, large sample sizes are needed to find a statistically significant finding. Furthermore, the focus in behavioral teratology is on the predictive power of the prenatal substance exposure after taking other covariates into account (Streissguth et al., 1989).

One should keep in mind that alternative explanations might be responsible for the findings as well. For instance, it is possible that an underlying genetic factor may account for both the lifestyle habits of the pregnant mother and her offspring's neurodevelopment. Ramsay and Reynolds (2000) suggested that women who smoke during pregnancy might possess a constellation of personality traits that distinguishes them from other women. They may have less control over their behavior, a trait that may accompany either hyperactivity or compulsiveness. Another possibility, according to Ramsay and Reynolds (2000) is that maternal smoking during pregnancy may accompany an elevated antisocial trait with reduced concern for other people and reduced awareness of the consequences of one's conduct, resulting in disregarding the consequences of smoking for one's infant. Thus, the personality of pregnant smokers may reflect a familial vulnerability for later disorders. In addition, Hill et al. (2000) suggested that familial loading for alcohol dependence is an important risk factor for the development of childhood psychopathology and may account for reported associations between prenatal exposure to nicotine and alcohol.

Finally, in interpreting the results, care should be taken with regard to non-response bias with selective drop-outs during longitudinal studies (Rothman and Greenland, 1998).

4. Smoking during human pregnancy

In the United Kingdom, over a quarter of pregnant women who smoke continue to do so during pregnancy (Coleman, 2004). Also in the United States, despite abundant adverse publicity, tobacco use occurs in about 25% of all pregnancies (Bardy et al., 1993; DiFranza and Lew, 1995). Most of these women are young, unmarried and from low socioeconomic strata (Kvale et al., 2000).

Several reports have established that maternal smoking during pregnancy is adversely associated with neurobehavioral and cognitive outcomes. This review mainly focuses on studies that have established a dose–response relationship between prenatal maternal smoking and offspring outcome. As can be concluded from these studies, the association between low to moderate amounts of smoking during pregnancy and offspring outcomes can often be found in a dose–response way.

4.1. Neurobehavioral outcomes related to prenatal maternal smoking

Two recent reviews have clearly described neurobehavioral associations with prenatal maternal smoking (Ernst et al., 2001; Linnet et al., 2003). Their findings are summarized and results from a few recent studies are added. Many of the studies discussed below employed multivariate statistical analyzes to control for many potential confounders of the association between prenatal nicotine exposure and children's behavior and cognition.

Overall, the effects of maternal smoking during pregnancy and neurobehavioral effects in young infants (age 2 or younger) have been inconsistent (Ernst et al., 2001). This may be due to less sensitive assessment tools for this age group, or incomplete brain maturation and deficits, therefore, may not have been detectable. More studies have focused on childhood and adolescent outcomes. However, as the child gets older, the postnatal environment is likely to exert a greater influence on the outcomes of interest (Fried, 2002). As described earlier in this paper, the possibility of postnatal exposure to smoking should be considered as well, although not all studies have done so or reported this possibility.

Fried and Makin (1987) have reported increases in hypertonicity and heightened tremors and startles among neonates who were prenatally exposed to tobacco compared to neonates born to non-smokers. In line with these findings, a recent small prospective study, including 27 nicotine exposed and 29 unexposed full-term newborn infants, found that the nicotine exposed newborns were more excitable and hypertonic and showed more stress/abstinence signs on a standard neurobehavioral assessment (Law et al., 2003). One study found that negative affect of 2-year-olds, as measured by maternal report on a questionnaire, was related to maternal smoking during pregnancy (Brook et al., 2000). Since it has been shown that adverse birth outcome, such as

preterm birth, is related to neurologic and developmental disabilities in the infant during the first 2 years of life (e.g. Marlow et al., 2005), it should be noted that only Law et al. (2003) adjusted their findings for factors relating to birth outcome.

Neurobehavioral outcomes of interest in childhood have mostly been Attention Deficit Hyperactivity Disorder (ADHD) and other externalizing behaviors. In a recent review, Linnet et al. (2003) described 24 studies that evaluated the association between smoking during pregnancy and ADHD or ADHD symptoms. Most studies assessed prenatal exposure retrospectively, did not use validated diagnostic criteria of ADHD, nor adjusted for familial psychopathology. However, eight well-designed studies were identified (O'Connor et al., 1997, 2002b; Williams et al., 1998; Bor et al., 1997; Fried et al., 1992b; Naeye and Peters, 1984; Nichols and Chen, 1981; Streissguth et al., 1984), and reported small but independent effects of smoking on a variety of symptoms related to ADHD in 4–7-years-old children. Four of those studies found a dose–response-like association (Williams et al., 1998; O'Callaghan et al., 1997; Naeye and Peters, 1984; Nichols and Chen, 1981). In line with these studies, a recent prospective birth cohort of 9357 children provided strong evidence for a dose–response relationship between maternal smoking during pregnancy and hyperactivity in 8-year-old children (Kotimaa et al., 2003).

While Linnet et al. (2003) focused specifically on ADHD in their review, other studies have focused on other aspects of externalizing (e.g. oppositional and aggressive) behavior as well. Orlebeke et al. (1999) tested 1,377 2–3-year-old twin pairs with the Child Behavior Checklist (CBCL) and found that maternal smoking during pregnancy was associated with a significant increase in externalizing behavior in general, but most particularly with aggression. Wasserman et al. (1999) found similar results for 4–5-year-olds. Day et al. (2000) found an association of third trimester prenatal nicotine exposure with oppositional behavior in children at age three.

Of interest are two recent studies that tested the association between maternal smoking during pregnancy and ADHD or conduct problems in twin offspring (Thapar et al., 2003, and Maughan et al., 2004, respectively). By using a twin design, both studies were able to take into account the effects of genetic factors that may explain the behavioral outcomes in children. Thapar et al. (2003) used a population-sample of 1452 twin pairs, aged 5–16, whose mothers retrospectively reported maternal smoking behavior during pregnancy. The findings showed a strong contribution of genetic factors with regard to ADHD-symptoms, on top of which maternal smoking during pregnancy was able to explain some additional variance. Maughan et al. (2004) used data from a population sample of 1116 twin pairs, aged 5–7 years, and found that strong initial effects of prenatal smoking on conduct problems in the children, were reduced strongly by controlling for both

genetic and environmental risks. These authors conclude that women who smoke during pregnancy are different from non-smokers with regard to personality factors (they were more antisocial and more depressed), and environmental factors (they had more SES disadvantage).

Ernst et al. (2001) concluded in their review that for adolescents and young adults an increased incidence of ADHD, conduct disorder, or criminality (in adulthood) was found after prenatal maternal smoking. There is evidence of consistent dose–response relationships, in which increasing exposure to maternal smoking during pregnancy is associated with increased rates of externalizing behavior (Fergusson et al., 1998). However, the measure of maternal smoking in pregnancy was obtained retrospectively in most studies, and it is difficult to separate the effects of smoking from other confounding environmental and genetic factors. For instance, a study of Milberger et al. (1997) showed that smoking was found to be familial among ADHD families, but not among control families. This suggests that a common genetic vulnerability factor for smoking and ADHD may provide another explanation for the increased rate of ADHD among the offspring of smokers. Also, maternal postnatal smoking may be of influence. In a large cohort study of more than 13,000 children, it was found that the highest risk for childhood-onset conduct problems were for children whose mother not only smoked heavily in pregnancy, but who also continued to smoke after birth (Maughan et al., 2001). A recent large birth cohort of 4169 males and 3943 females, found a dose–response relationship between maternal self-reported daily smoking during pregnancy and both criminal arrest and psychiatric hospitalization for substance abuse disorder in male and female offspring, after adjusting for various covariates, such as parental criminal history and parental psychiatric hospitalization (Brennan et al., 2002).

Finally, other epidemiological studies have also indicated that maternal smoking during pregnancy may induce a predisposition in the offspring to early onset of smoking (Ernst et al., 2001; Kandler et al., 1994; Cornelius et al., 2000; Buka et al., 2003), although this effect may only be found after intrauterine exposure to heavy smoking. For instance, Cornelius et al. (2000) found that 10-year-old offspring exposed to more than 1/2 pack of cigarettes per day in utero had a 5.5-fold increased risk for early experimentation. Unfortunately, until now, no follow-up study of this cohort has been published. In a 30-year prospective study Buka et al. (2003) found that offspring exposed to one pack or more of cigarettes for 1 day or more during pregnancy had an elevated risk of developing nicotine dependence. No such relationship was found for lower levels of smoking during pregnancy in this study.

4.2. Cognitive function after prenatal maternal smoking

Two studies have shown cognitive deficits in the young age group after in utero exposure to nicotine. A decrease in

motor scores and verbal comprehension was found in 13-months-old offspring (Gusella and Fried, 1984), and reduced auditory acuity has also been reported (Saxton, 1978). A few studies have focused on cognitive function of children (aged 3–7 years) after in utero exposure to nicotine. Sexton et al. (1990) found a lower score on general cognitive functioning in 3-year-old children of mothers who smoked 10 or more cigarettes throughout pregnancy as compared to children whose mothers quit smoking during pregnancy. Sustained attention, response inhibition, and memory were affected in 6-year-olds, and lower overall cognitive function and receptive language were found (Fried et al., 1992a,b). Recently, prospective evidence from a Dutch birth cohort was found for a dose–response relationship between maternal smoking during pregnancy and lower scores on arithmetic and spelling tasks of children between 5.5 and 11 years of age (Batstra et al., 2003). In line with these studies, a study that compared a group of 6–17-year-old boys with ADHD with their first-degree relatives and healthy control subjects showed that children whose mothers smoked during pregnancy had significantly lower IQ scores than children whose mothers did not smoke (Milberger et al., 1998). Moreover, a prospective cohort study showed that prenatal nicotine exposure was significantly related to deficits in verbal learning and design memory, problem solving, and a slower response in eye-hand coordination in 10-year-olds (Cornelius et al., 2001). Cornelius et al. (2001) assessed prenatal tobacco exposure by means of the average number of cigarettes smoked daily, and were therefore able to test for a dose–response relationship. While the explained variance in verbal learning was only 1% accounted for by prenatal nicotine exposure, those infants who were exposed to heavy prenatal smoking had an increased risk to perform in the below-average range. This finding was based on a calculation of the regression coefficients, which were then transformed into percentiles based on published norms. This may hamper optimal performance in the classroom in a serious way (Cornelius et al., 2001). More specific cognitive deficits in infants born to mothers who smoked during pregnancy have also been found. At 6–11 years of age, children prenatally exposed to nicotine were shown to have central auditory processing and visual-perceptual processing deficits (for an overview, see Fried, 2002).

Not all studies have found a negative relationship between prenatal maternal smoking and cognitive outcome in children. For instance, a large prospective study found no dose–response relationship between in utero nicotine exposure during the third trimester and cognitive performance in 5-year-olds (Eskenazi and Trupin, 1995).

4.3. Prenatal smoking effects in animal pregnancy

In most animal studies, pregnant animals received nicotine throughout their pregnancy, precluding the ability to identify specific periods of increased fetal vulnerability to

nicotine effect. In addition, because nicotine administration was discontinued after delivery in most animal studies, potential maternal nicotine withdrawal after delivery might have affected maternal care of offspring (Ernst et al., 2001). In spite of the wide variability of study designs employed, the findings of these animal studies have been quite similar.

In a recent review, Ernst et al. (2001) have described the findings of neurobehavioral effects of in utero exposure to nicotine in animals. Of interest are results showing an enhanced locomotor activity related to in utero nicotine exposure across species (rats, mice, and guinea pigs), and cognitive impairment, such as attention and memory deficits in performance on various maze tasks. Furthermore, animal studies have demonstrated deficits in learning tasks in prenatally exposed animals. These findings are consistent with the cognitive deficits found in psychiatric disorders such as ADHD (Ernst et al., 2001). Thus, the effects on neurobehavioral outcome in animal studies are in line with results from human studies.

A recent study of prenatal exposure to nicotine in rats showed alterations in the subsequent response to subcutaneous infusion of nicotine in adolescent offspring, reflected by persistent cholinergic hypoactivity, which worsened during nicotine withdrawal. In humans, this may contribute to the increased risk of later smoking behavior after prenatal nicotine exposure (Abreu-Villaca et al., 2004).

4.4. Mechanisms related to prenatal smoking and offspring outcomes

Cigarette smoking during pregnancy results in fetal exposure to large amount of toxic components, such as nicotine, carbon monoxide, ammonia, nitrogen oxide, lead, and other metals. It would, therefore, be too simplistic to limit the fetal toxicity of cigarette smoke to nicotine (Ferreiro and Dempsey, 1999). However, most studies among animals have focused on the effects on the offspring of prenatal nicotine exposure. In humans, nicotine passes rapidly and completely across the placenta, with fetal concentrations generally being 15% above maternal levels (Walker et al., 1999). Cigarette smoke interferes with normal placental function, reducing uterine blood flow. The fetus is deprived of nutrients and oxygen, resulting in episodic fetal hypoxia–ischemia and malnutrition (Suzuki et al., 1980), which may result in intrauterine growth retardation often seen in infants born to smoking mothers.

Furthermore, nicotine acts as a neuroteratogen that interferes with the developing nervous system (Levin and Slotkin, 1998). The direct effects result from interactions of nicotine with nicotinic acetylcholine receptors (nAChRs), which are present very early in the fetal human brain (Hagino and Lee, 1985). Periods of transient high receptor density have been reported in the frontal cortex, hippocampus, cerebellum, and brainstem during mid-gestation and neonatal periods (Hellström-Lindh and Nordberg, 1998). Also, products of cigarette smoke, such as carbon

monoxide and ingredients in tobacco tar, can directly affect the fetal brain (Ernst et al., 2001).

It has been suggested that fetal exposure to nicotine results in a premature switch from cell replication to differentiation of the target cells by cholinergic stimulation (Ernst et al., 2001). In addition, animal studies have shown that the cholinergic neurotransmitter system may be affected by prenatal nicotine exposure. Prenatal nicotine exposure produced persistent cholinergic hypoactivity throughout adolescence and adult life (Abreu-Villaca et al., 2004). Alterations at this neurotransmitter level could account for the development of learning and memory deficits (Steckler and Saghal, 1995).

Also, some studies indicated effects of prenatal nicotine exposure on neurotransmitter systems in the offspring. For instance, the noradrenergic and dopaminergic systems have been found to be hypoactive and hyporesponsive to exogenous postnatal nicotine stimulation after prenatal nicotine exposure (e.g. Slotkin, 1998).

A recent study exposed pregnant mice to a combination of alcohol and nicotine and found that a decreased enzyme-mediated antioxidative system could account for the oxidative stress caused by the prenatal substance exposure (Li and Wang, 2004). Oxidative stress may produce cell damage, especially in the brain, which is vulnerable to a lack of oxygen (Rougemont et al., 2002). This may result in more general deficits in behavior and development.

Another potential mechanism involved in the effects of prenatal smoking on neurobehavioral outcome may be a dysregulation of the fetal hypothalamic-pituitary-adrenal (HPA) axis, because alterations in the HPA-axis may be involved in the development of psychopathology (Huizink et al., 2004). These alterations in the HPA-axis may reflect an increased vulnerability of the individual to environmental challenges in later life, and may sensitize for drug-seeking behaviors as well (Sarnyai et al., 2001; Koob, 1999). Thus, rather than resulting in specific effects, dysregulation of the HPA-axis may be involved in a general vulnerability for developmental psychopathology (Huizink et al., 2004) and a tendency to increased substance use (Goeders, 2003). One human study showed that 2-month-old infants exposed in utero to cigarettes had higher basal HPA-axis activity, as reflected by increased basal cortisol levels, and had attenuated responses to stress than non-exposed infants, whereas the same infants showed a trend towards a higher basal HPA-axis activity at 6 months of age (Ramsay et al., 1996). No animal studies have been published yet on the potential effect of prenatal nicotine exposure on the HPA-axis reactivity.

5. Alcohol use during human pregnancy

Alcohol is widely recognized as a teratogenic agent causing CNS dysfunction and impaired mental functioning. The most serious consequence of maternal drinking during

pregnancy is fetal alcohol syndrome (FAS), the diagnosis of which is based on three criteria: (1) growth deficiency manifested by small overall height and small head size; (2) central nervous system disorders, including mental retardation and (3) a distinctive pattern of abnormal facial features. Alcohol exposure during pregnancy has the potential to disrupt the proper sequence of neural development and thus negatively affect cognitive development in children (Willford et al., 2004).

The majority of studies have focused on the (long-term) effects of heavy drinking during pregnancy and its relation to FAS and adverse outcomes. It is only recently that prospective studies have been conducted to determine whether moderate alcohol exposure during pregnancy has effects on the offspring's neurobehavioral and cognitive outcomes. These studies will be reviewed below.

5.1. Neurobehavioral effects of prenatal (moderate) maternal drinking

Streissguth and her research group have reported adverse neurobehavioral effects related to varying levels of prenatal alcohol exposure in the neonatal period, at 8 months, at 4 years of age and ages up to adolescence (e.g. Streissguth et al., 1984, 1989, 1990, 1996; Olson et al., 1997; Baer et al., 2003). After exposure to low doses of prenatal alcohol more (maternal-reported) hyperactivity was found in 4-year-olds, although the clinically suspect behaviors were increased only after heavy prenatal alcohol exposure (Streissguth et al., 1989). Jacobson et al. (1994) showed evidence of longer reaction times in children after moderate prenatal alcohol exposure.

Other behavioral outcomes related to prenatal alcohol exposure include psychosocial deficits and problem behaviors, which have been found both in FAS children and in children who were prenatally exposed to moderate levels of alcohol. These children appear to be at increased risk for psychiatric disorders, trouble with the law (Streissguth et al., 1996), were likely to be rated as hyperactive, disruptive, impulsive or delinquent (Roebuck et al., 1999). In addition, adverse effects of prenatal alcohol exposure on child behavior, aggressive and externalizing behavior in particular, at age 6–7 years were found evident even at low levels of exposure (i.e. one alcoholic beverage a week), and showed dose-response effects after careful control for confounding factors (Sood et al., 2001). However, Linnet et al. (2003) reviewed nine studies with regard to ADHD as outcome of in utero alcohol exposure and concluded that the results were inconsistent (for details, see Linnet et al., 2003). However, most of these studies used dichotomized exposure measures of alcohol intake (abstaining from alcohol versus one or more drinks per day/week). The studies that have found associations between prenatal moderate alcohol exposure and neurobehavioral outcomes report that the amount of variance uniquely accounted for by prenatal alcohol exposure ranges between 0.6 and 2%

(Sood et al., 2001; Jacobson and Jacobson, 2002). In fact, the pattern of maternal drinking seems to be of importance, since results from various studies indicate that even a single ‘binge’ drinking event (five drinks/occasion/week) in early pregnancy could have a significant impact on developmental outcomes of the offspring, including perinatal brain injury and learning problems (Eckardt et al., 1998).

In adolescence, fetal exposure to alcohol may also result in specific sensitivity and drug preferences. A prospective study of more than 400 subjects indicated that prenatal alcohol exposure was associated with alcohol problems at 21 years of age, after controlling for family history of alcohol problems and other covariates, such as parental use of other drugs (Baer et al., 2003). Also Streissguth et al. (1996) found alcohol and other drug abuse in offspring prenatally exposed to moderate levels of alcohol. Adult offspring exposed to heavy levels of alcohol in utero had a prevalence rate of 35% to develop alcohol or drug problems, besides other adverse life outcomes (Streissguth et al., 2004). Another study suggested that the impact of maternal drinking during pregnancy on the drinking behavior of adolescent offspring may be sex-specific, with elevated risk for female offspring only (Griesler and Kandel, 1998). Furthermore, social behavior deficits, such as antisocial and delinquent behavior, have been associated with prenatal alcohol exposure in adolescents and adults without the full FAS diagnosis and at lower doses of alcohol than would be necessary to produce the full FAS (Carmichael-Olson et al., 1997).

5.2. Cognitive function after prenatal maternal drinking

A recent meta-analysis showed that fetal alcohol exposure, at moderate to heavy dosage levels, was associated with significantly lower Mental Developmental Index scores from the Bayley Scales of Infant Development (BSID; Bayley, 1969) among 12–13-month-old-infants (Testa et al., 2003). An average decrement in Mental Developmental scores (MDI) of more than 8 points, or about half a standard deviation, was found among children whose mothers consumed two or more drinks per day during pregnancy (Testa et al., 2003). At lower dosage level there was no effect. The meta-analysis did not show a similar association in younger (6–8 months) or older (18–24 months) infants. Therefore, the authors suggest that specific item content of the MDI assessment at age 12–13 months (visual perception, spatial relations, short-term memory and attention, receptive language) appears to be sensitive to prenatal alcohol exposure. In childhood, a few studies have demonstrated that moderate alcohol exposure is associated with some deficits in children, including IQ decrements and learning problems, and deficits in information processing speed. For instance, Carmichael-Olson et al. (1997) reported that social drinking (a little less than two drinks per day) was associated with learning deficits in children. Streissguth et al. (1989, 1990) found decreases in IQ in relation to

moderate alcohol exposure. At 4 years of age, a subtle decrease in IQ of nearly five points was found (Streissguth et al., 1989) and at age 7 a 6-point decrement in IQ was found (Streissguth et al., 1990). In addition, decrements in speed of information processing and sustained attention were found after prenatal alcohol exposure in 4-year-olds (Streissguth et al., 1989). In contrast, another study showed that low levels of prenatal alcohol exposure were not related to cognitive outcomes in 3–6-year-old children (Fried and Watkinson, 1990; Fried et al., 1992a).

Furthermore, a study reported that daily alcohol use during the first and second trimesters of pregnancy predicted poorer performance on verbal learning and verbal and visual memory tasks in 10-year-olds (Richardson et al., 2002). Similar effects were found in the same children when they were 14 years of age for first trimester alcohol exposure (Willford et al., 2004). Therefore, the authors concluded that a consistent pattern of long-term impairment in learning and memory function was found after prenatal exposure to light to moderate alcohol levels in the first trimester of pregnancy. They also suggested that these are latent effects of prenatal alcohol exposure that are expressed as the central nervous system develops and matures, because the learning and memory deficits were not detected at younger ages in the same prenatally alcohol exposed offspring (Willford et al., 2004). In line with these studies, Olson et al. (1997) reported a significant association between ‘social drinking’ levels during pregnancy and learning problems rated by school achievement in early adolescence.

A methodological issue related to the aforementioned studies is the observation that in humans, several groups of pregnant drinkers may be differentiated. For instance, those who drink only early in pregnancy and then stop possess positive characteristics that promote more optimal child outcomes, including more prenatal visits, lower gravidity, and fewer depressive symptoms (Day et al., 1999). These factors may contribute to a normal cognitive and behavioral development of the child, although exposure to alcohol early in pregnancy still may be regarded as a risk. In contrast, those who continue to drink throughout pregnancy are more likely to be unmarried, smokers, and marijuana users (Day et al., 1999) and therefore, children born from these mothers may be exposed to a variety of risk factors, including prenatal alcohol exposure.

5.3. Alcohol effects in animal pregnancy

While most animal studies have used heavy levels of alcohol (ethanol) exposure, a few recent studies have described effects on the offspring after moderate prenatal alcohol consumption. For instance, Savage et al. (2002) showed that moderate prenatal alcohol exposure in rats elicited subtle, yet significant learning deficits in offspring when confronted with the Morris Water Task. In a review that described the comparability of human and animal models with regard to prenatal alcohol exposure,

Driscoll et al. (1990) reported deficits in learning, inhibition, attention, regulatory behaviors, and motor performance. The authors stated that perhaps the most common finding following prenatal alcohol exposure in animal studies is an increased level of activity or exploration. The magnitude of these effects was generally dose-related. Of interest is a recent study that described a mouse model of prenatal ethanol exposure using a voluntary drinking paradigm (Allen et al., 2003). In such a model, the effects of moderate prenatal exposure to ethanol can be examined, without imposing additional stress to the pregnant animals caused by intubation or injection, because the ethanol was consumed voluntarily. The offspring of these mice showed increased exploratory behavior.

In 6-months-old monkeys, prenatal exposure to moderate levels of ethanol (one or two drinks per day), was related to disturbed attention and neuromotor development (Schneider et al., 2004). Clarren et al. (1992) showed that once-a-week binge drinking during early gestation (a dose comparable to six drinks) in pigtailed macaques caused behavioral abnormalities similar to the effects found after drinking throughout pregnancy. Schneider et al. (2001) have confirmed that early pregnancy is a period of vulnerability with regard to the effects of prenatal alcohol exposure on neurobehavior in the offspring. In particular, orientation (or attention) and motor maturity were affected in non-human primate offspring after prenatal exposure to moderate levels of ethanol in early pregnancy.

5.4. Mechanisms related to prenatal maternal drinking and offspring outcomes

Alcohol is freely distributed from a pregnant woman's blood to the fetus. It crosses both the placenta and the fetus' blood–brain barrier rapidly and easily (Julien, 1998). Rodent studies have found that exposure to alcohol during the period of high synaptogenesis (equivalent to the second and third trimesters of human pregnancy) produces several alterations in brain development, e.g. neuronal loss, altered neuronal circuitry, and apoptotic neurodegeneration in the developing forebrain (Miller and Potempa, 1990; West and Hamre, 1985; Ikonomidou et al., 2000). In addition, animal studies have shown dose–response related effects of prenatal alcohol exposure on the morphology of the corpus callosum (Qiang et al., 2002), and glutamatergic neurotransmitter function in the hippocampus (Savage et al., 2002), which diminishes hippocampal plasticity and learning. These studies show effects of prenatal alcohol exposure at doses much lower than previous studies. Zhou et al. (2003) reported that in mice the neural tube midline is highly vulnerable to alcohol during development and can result in compromised neural tube midline, which may be any deviation from proper neural tissue formation and maturation in the midline. Characteristic deficits in the midline tissue are a common teratogenic feature of FAS. However, the results of Zhou et al. (2003) suggested that even

a moderate blood level of alcohol caused a high frequency of neural tube midline defects during early development, resulting in abnormal neural development, which may contribute to subtle neurodevelopmental deficits.

In line with these animal studies, structural brain imaging in humans has revealed several differences between the brains of prenatally alcohol-exposed and non-exposed individuals. Most of these studies have focused on FAS children as compared to controls. Thus, the findings reflect effects of heavy prenatal alcohol exposure and may not be found, or to a lesser extent, after low or moderate prenatal alcohol exposure. However, some of the animal studies suggested that the findings might be a result of moderate alcohol exposure as well. The structural brain imaging studies in humans found disproportionately reductions in the basal ganglia, mostly in the caudate nucleus, which may account for the alterations in cognitive functioning after prenatal exposure to alcohol (Mattson et al., 1996; Archibald et al., 2001). For instance, the caudate nucleus has extensive neural connections to the frontal lobes of the brain, the part of the brain that may mediate higher cognitive and executive functions. In addition, corpus callosum thinning and displacement has been found in children, adolescents, and young adults prenatally exposed to alcohol (Roebuck et al., 1998; Sowell et al., 2001), which may account for verbal learning deficits (Sowell et al., 2001). Also, reduced cerebellar size has been found (Sowell et al., 1996), which may relate to learning deficits. In addition, volume asymmetries in the hippocampus of prenatally alcohol-exposed children were found (Riikonen et al., 1999), which may account for memory deficits. Furthermore, brain mapping techniques detected disproportionate reductions in the brain's white matter, particularly in the parietal lobe, which is involved in visual-spatial processing and in the integration of sensory information (Archibald et al., 2001; Sowell et al., 2001).

Whereas structural imaging determines the size of a particular brain structure only, functional imaging techniques allow researchers to study how the brain works. Only a small number of studies have used the latter techniques in children, because of the technical difficulties. Electroencephalography (EEG) studies have suggested that the sensory information processing is affected in FAS children (e.g. Kaneko et al., 1996). One Positron Emission Tomography (PET) study revealed reduced metabolic activity in the caudate nucleus and in the thalamus of FAS adolescents while resting (Clark et al., 2000). One Single Photon Emission Computed Tomography (SPECT) study showed that the normal left-right dominance in metabolic activity of FAS children was lacking. In particular, SPECT revealed mild hypoperfusion of the left parietooccipital region, which may support verbal or language deficits in these children (Riikonen et al., 1999). One functional Magnetic Resonance Imaging (fMRI) study suggested that a working memory task was more difficult for prenatally alcohol-exposed

adults, requiring greater involvement of the dorsolateral prefrontal cortex (Connor and Mahurin, 2001).

Besides these effects, exposure to alcohol in utero in animals reflected alterations in stress response indices, such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis reactivity to stress in offspring, in the absence of alterations in basal hormone levels (e.g. Schneider et al., 2002; Kim et al., 1999; Spear, 1996; Nelson et al., 1986; Taylor et al., 1982; Weinberg, 1989). A study in human infants by Jacobson et al. (1999) reported higher poststress cortisol levels in 13-months-old infants who were exposed prenatally to high levels of alcohol. As noted before, these alterations in HPA-axis regulation may be involved in the development of psychopathology (Huizink et al., 2004) and may sensitize for drug-seeking behaviors as well (Sarnyai et al., 2001; Koob, 1999).

6. Cannabis use in human pregnancy

Cannabis is the most commonly used illicit drug among women of reproductive age and in the United States the self-reported use of this substance is 2.9% during pregnancy (National Pregnancy and Health Survey, 1996; Ebrahim and Gfroerer, 2003).

Fried (2002) has reviewed the studies on behavioral teratologic consequences of prenatal exposure to cannabis. Only two longitudinal cohorts with very different sample characteristics were found that examined the possible impact of cannabis exposure in utero on neurobehavioral and cognitive outcomes in offspring beyond early school age. The Ottawa Prenatal Prospective Study (OPPS; Fried, 2002) examines the consequences of cannabis (and smoking) use during pregnancy in a sample of low-risk, white, predominantly middle-class families, as yet up to the age of 18–22 years. The Maternal Health Practices and Child Development Study (MHPCD; Richardson and Day, 1998) has been following a high-risk cohort of low socioeconomic status, started in 1982, and has reported offspring outcome up to the age of 10. These cohorts have mainly described the impact of heavy cannabis use on offspring outcome. At present there are no studies that have focused on moderate cannabis use during pregnancy.

6.1. Neurobehavioral outcomes after prenatal cannabis exposure

In the neonatal period, findings from the OPPS and MHPCD showed that there may be an association between aspects of nervous system functioning and prenatal exposure to marijuana, reflected by increased tremors that were typically accompanied by exaggerated and prolonged startles (Fried and Makin, 1987) or altered sleep patterns (Richardson et al., 1989). The Maternal Life Style study, a clinical prospective study of acute neonatal events and long-term health and developmental outcomes associated with

prenatal cocaine exposure, also included prenatal marijuana exposure. More stress/abstinence signs were found in 1-month-old infants of mothers who used low to moderate amounts of cannabis in pregnancy (Lester et al., 2002).

At the 6-year-follow up, the OPPS reported more impulsive and hyperactive behavior of children prenatally exposed to cannabis (Fried et al., 1992b). The MHPCD cohort showed that at 6 years of age, prenatally cannabis exposed children were rated by their teachers as showing more delinquent behavior (Leech et al., 1999). Moreover, the 6-year-old children showed more impulsive behavior at a continuous performance task (Leech et al., 1999). At age 10, these children had hyperactivity, increased inattention, impulsivity and delinquency symptoms as reported by their mother and their teachers (Goldschmidt et al., 2000). Also, attention deficits were found, which may mediate the relation between prenatal cannabis exposure and delinquency (Goldschmidt et al., 2000).

None of these studies have focused on substance (ab)use by the offspring after prenatal exposure to cannabis.

6.2. Cognitive function after prenatal cannabis exposure

In the OPPS, no association was found between prenatal cannabis exposure and infant mental or motor development at 1 year of age (Fried and Watkinson, 1988). The high-risk MHPCD cohort, however, showed an association between the use of 1 or more joints per day in third trimester pregnancy and a decrease in mental scores of the Bayley Scales of Infant Development (Bayley, 1969) at 9 months of age, which disappeared at 18 months (Richardson et al., 1995).

When the offspring of OPPS reached the age of 4, associations between regular (more than 5 joints a week) prenatal cannabis exposure and significantly lower scores on several verbal and memory subscales of the McCarthy Scales of Children's Ability were noted (Fried and Watkinson, 1990; McCarthy, 1972). Similar findings applied to the offspring of the MHPCD cohort at 3 years of age, in which an impairment on short-term memory, verbal and abstract/visual reasoning was found after in utero exposure to cannabis (Day et al., 1994).

As the children get older, the most striking finding is that 'executive function' (EF), an overarching cognitive domain reflecting the ability to organize and integrate specific cognitive and output processes over an interval of time, may be hampered. EF is involved in, e.g. cognitive flexibility in problem solving, sustained and focused attention, and working memory. Specific tests from the WISC-II, such as the Block Design and Picture Completion, requiring higher order cognitive processes which are part of EF, were performed less well by prenatal cannabis exposed 9- and 12-year-olds from the OPPS cohort (Fried et al., 1998). This is consistent with findings from the MHPCD cohort, that showed problems in abstract and visual reasoning, and more inattention and impulsivity, at 10 years of age after prenatal

cannabis exposure (Richardson and Day, 1997; Richardson et al., 2002). Fried and Watkinson (2000) examined visuoperceptual functioning in greater detail in the 9–12-year-old OPPS subjects and found more support for impaired aspects of EF (e.g. visual-motor integration, non-verbal concept formation, and inhibition of prepotent responses) after prenatal cannabis exposure. At 13–16 years of age, however, prenatal cannabis exposure was not associated with aspects of attention, such as flexibility, encoding and focusing (Fried et al., 2003).

6.3. Cannabis effects in animal pregnancy

Navarro et al. (1995) have reviewed behavioral consequences of maternal exposure to cannabinoids in rat models and concluded that it resulted in alteration in the pattern of ontogeny of spontaneous locomotor and exploratory behavior in the offspring. Adult animals exposed during gestational and early neonatal periods, when lactation took place, showed persistent alterations in the behavioral response to novelty, social interactions, sexual orientation and sexual behavior. They also exhibited a lack of habituation and reactivity to a variety of stimuli. Also, visual developmental milestones were delayed in rodents after prenatal exposure to cannabis (Borgen et al., 1973; Fried, 1976). In addition, Mereu et al. (2003) found a disruption of memory retention and hyperactive behavior in offspring of rats who were administered with a cannabinoid receptor agonist during pregnancy. Moreover, the offspring appeared to be sensitized to reinforcing effects of morphine, suggesting an increased sensitivity to addictive behavior.

6.4. Mechanisms related to prenatal cannabis use and offspring outcomes

Cannabinoids, the psychoactive ingredients of cannabis, can cross the placental barrier (Gomez et al., 2003). This way, cannabinoids are able to affect the expression of key genes for neural development leading to neurotransmitter and behavioral disturbances (Gomez et al., 2003). Furthermore, the early presence of cannabinoid receptors during fetal brain development provides a mechanism by which cannabinoids might produce the effects found in the offspring (Navarro et al., 1995). Animal research indicates that endogenous cannabinoids and their cannabinoid CB1 and CB2 receptors are involved in embryonal implantation, neural development, and the initiation of suckling in the newborn (Fride, 2004). Also, cannabinoid CB1 receptors have been found in the human placenta (Park et al., 2003), and may mediate adverse actions of prenatal cannabis exposure. One of the major cannabinoid receptor sites in the human brain is in that part of the forebrain that is associated with higher cognitive functions (Glass et al., 1997) as well as in the cerebellum. This may support the suggestions that prenatal cannabis exposure is related to deficits in specific higher order cognitive functions. In line with this theory are

findings from a recent study on the OPPS offspring aged 18–22-years-old, using fMRI to test prefrontal cortex activity by using Go/No-Go paradigms to assess response inhibition (Smith et al., 2004). An increased activity in the left orbital frontal gyrus and right dorsolateral of the prefrontal cortex was found. The authors suggested that this result might reflect increased effort to perform the response inhibition task, which may be caused by a delayed development of this brain area. However, more studies are needed.

Other mechanisms that have been proposed originate from animal models. For instance, prenatal cannabinoid exposure influences gene expression on a key protein for brain development, the neural adhesion molecule L1, which plays an important role in processes of cell proliferation and migration, and synaptogenesis (Gomez et al., 2003). Furthermore, prenatal cannabinoid exposure altered the normal development of nigrostriatal and mesolimbic dopaminergic neurons (Rodriguez de Fonseca et al., 1991). These mechanisms may underlie the associations between prenatal exposure to cannabis and neurobehavioral and cognitive outcomes.

With regard to the HPA-axis, Del Acro et al. (2000) observed long-lasting changes in the HPA axis reactivity in rat offspring exposed in utero to a synthetic cannabinoid compound. Offspring prenatally exposed to high levels of a synthetic cannabinoid compound showed a decreased responsiveness of the HPA axis to stressors at adult ages, whereas offspring prenatally exposed to low levels of the same cannabinoid compound showed a sensitization of the HPA axis. The latter may underlie some of the behavioral changes found in the moderately exposed offspring.

7. Discussion

Most studies included in this review indicate that low to moderate maternal smoking, or drinking and (heavy) cannabis use during pregnancy may contribute to neurobehavioral and cognitive deficits in human offspring. However, because of several methodological limitations no causal conclusions can be drawn. One of the most fundamental issues regarding interpretation of these results of human studies is the inability to manipulate a range of factors that potentially influence outcomes in the offspring in human studies. Therefore, it is of importance to take into account the findings of animal studies that permit control of environmental factors, in order to validate findings in humans.

Prenatal exposure to either maternal smoking, alcohol or cannabis use is related to some common neurobehavioral outcomes, including symptoms of ADHD (inattention, impulsivity) and increased externalizing behavior. Likewise, although information from human studies is scarce, it appears that adult animals exposed to alcohol, nicotine or cannabis in utero are more responsive to that same as well as other drugs of abuse (Malanga and Kosofsky, 2003).

A number of animal models suggest that in utero exposure to substances may lead to alterations in brain systems involved in addiction (Malanga and Kosofsky, 2003). It may, therefore, be of interest to test these hypotheses in well-designed prospective long-term longitudinal human studies. Also, common cognitive outcomes may be found after exposure to either prenatal maternal smoking or drinking, reflected by decreased general cognitive functioning, and deficits in learning and memory tasks. Support for these findings comes from animal studies, which show similar results. The effects found after prenatal exposure to moderate levels of alcohol, smoking, or (heavy) cannabis use, may be regarded as subtle effects. However, even subtle effects can have both short- and long-term implications. The short-term importance of these differences may be the reflection of neurobehavioral vulnerability of these children, which may be exacerbated by the care giving environment (Lester et al., 2002). These subtle and sometimes even inconsistent findings demonstrate the importance of employing sensitive endpoints for behavioral teratology studies (Driscoll et al., 1990). In fact, these subtle effects after moderate exposure are in line with the dose–response principle of behavioral teratology.

The consequences of mostly heavy prenatal exposure to cannabis are also subtle (Fried and Smith, 2001) and may be more specific. During infancy, there is little evidence as yet for a prenatal cannabis effect upon neurobehavioral or cognitive outcomes. However, beyond the age of 3, findings suggest that aspects of cognitive behavior (executive function), mediated by the prefrontal region of the brain may be negatively associated with prenatal cannabis exposure.

Besides these associations between maternal smoking, drinking or cannabis during pregnancy and neurobehavioral or cognitive outcomes, interaction effects of polydrug use may occur. The most commonly abused drugs, alcohol and nicotine, co-occur frequently (Ebrahim and Gfroerer, 2003). Moreover, the groups of substance (ab)users appear to share some adverse environmental factors, such as more social isolation, more single-parenthood, negative alterations in nutritional status, lower social background, and more problematic parental and family functioning. As was suggested for pregnant smokers by Ramsay and Reynolds (2000), pregnant substance users may share an elevated antisocial trait, which may reflect a familial vulnerability for later disorders. In addition, a genetic correlation appears to exist between nicotine and alcohol dependence. Less is known about low to moderate consumption of both substances in pregnancy and the associated interaction effects on the offspring.

Recent studies in monkeys have also shown that prenatal psychosocial stress may interact with the effects of prenatal substance abuse (e.g. Schneider et al., 1997; Roberts et al., 2004). The consequences of exposure to the combination of prenatal stress and moderate use of alcohol, nicotine or cannabis in human pregnancy are poorly understood

(Thadani, 2002). Schneider et al. (2002, 2004) have addressed one of these questions in a non-human primate model and found that prenatal exposure to moderate alcohol in combination with stress induced poor behavioral regulation during cognitive testing, such as increased activity levels. Schneider et al. (2004) also found reduced behavioral adaptation to stress after prenatal exposure to stress, alcohol, or both. Interestingly, some of the perturbations found after prenatal exposure to alcohol, in particular those reflecting alterations in stress response indices of the HPA-axis, appear to be partly similar to changes observed following exposure to prenatal stressors. It may, therefore, be useful to test for moderating, interacting, or even additive effects of prenatal alcohol exposure and prenatal stress exposure.

Little is known about the association between prenatal cannabis or nicotine exposure and the HPA-axis reactivity in offspring. Only one animal study has found effects on the HPA-axis reactivity after prenatal cannabinoid exposure (Del Acro et al., 2000), and, until now, only one human study was published on the relation between prenatal nicotine exposure and HPA-axis reactivity in offspring (Ramsay et al., 1996). If the HPA-axis reactivity is affected by (moderate) exposure to these substances, it may be a common underlying mechanism related to neurobehavioral outcomes.

Recently, it was suggested by Sullivan and Gratton (2002) that the right prefrontal cortex may be directly linked to stress-regulatory systems. Therefore, if prenatal substance exposures influence this particular part of the prefrontal cortex, alterations in the HPA-axis activity may occur. The findings from the OPPS studies suggest prefrontal cortex alterations after prenatal cannabis exposure. Also, ADHD patients have been reported to have lower right prefrontal cortex activity (for a review see Majewska, 2002). Since ADHD-symptoms appears to be a common outcome after prenatal exposure to various substances, it would be of interest to study the offspring with regard to their HPA-axis activity and right prefrontal cortex activity to gain more insight into the mechanisms involved in the neurobehavioral and cognitive deficits found after prenatal substance exposure.

In addition, of special interest is the hypothesis that prenatal substance exposure predisposes, perhaps by altering HPA-axis reactivity, to drug-seeking behaviors in adult offspring. This relation has been tested in animals. For instance, in a non-human primate model Higley et al. (1991) found correlations between increased stress behavior and HPA-axis activity on the one hand, and increased alcohol drinking on the other hand. Prenatal exposure to a substance may increase the later propensity for that specific substance, or for general substance abuse. Human studies suggest that a variety of prenatal substance exposures are related to offspring substance use. It is possible that certain stress system responses act either as a priming stimulus to increase craving for substances, or in drug-seeking behavior for

the purpose of self-medication (Majewska, 2002). Further systematic research in humans is warranted.

Exposure to substances such as alcohol, nicotine and cannabis may produce abnormalities in brain development. The behavioral impact of any such abnormalities that might occur depends on other pre- and post-natal factors, which may include genetic vulnerability. In addition, the HPA-axis reactivity may be altered due to prenatal alcohol, nicotine or cannabis exposure and may compromise the adaptation to postnatal environmental stressors. Strikingly similar results have been found after prenatal exposure to stress. Thus, the HPA-axis reactivity may explain some of the outcomes shared by these varying prenatal exposures. However, more research is still needed before definite conclusions can be drawn.

Of course, not all offspring show adverse outcomes after prenatal exposures. It is, therefore, of interest to study whether infants who have been exposed prenatally to any of these substances in utero have a milder phenotype if raised in healthy and supporting environments. If so, the specific environmental factors that might promote resilience can be studied (Kosofsky and Hyman, 2001).

Finally, the possibility of identifying a preventable prenatal risk factor for neurobehavioral and cognitive (subtle) deficits makes further research important for public health (Wakschlag et al., 2002).

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