Review

Postnatal environmental or experiential amelioration of neurobehavioral effects of perinatal alcohol exposure in rats

John H. Hannigan\textsuperscript{a,b,c,*}, Shonagh K. O’Leary-Moore\textsuperscript{b,d}, Robert F. Berman\textsuperscript{e}

\textsuperscript{a}Department of Obstetrics & Gynecology, Wayne State University, 275 East Hancock, Detroit, MI 48201, USA
\textsuperscript{b}Department of Psychology, Wayne State University, 275 East Hancock, Detroit, MI 48201, USA
\textsuperscript{c}C.S. Mott Center for Human Growth & Development, Wayne State University, 275 East Hancock, Detroit, MI 48201, USA
\textsuperscript{d}Brain Research and Imaging Neuroscience Program, Wayne State University, 275 East Hancock, Detroit, MI 48201, USA
\textsuperscript{e}Department of Neurological Surgery, University of California–Davis, One Shields Avenue, Davis, CA 95616, USA

Abstract

Fetal alcohol spectrum disorders (FASDs) in children are characterized by life-long compromises in learning, memory, and adaptive responses. To date, there are no clinical remedies for the treatment of global fetal alcohol effects, although interventions for specific outcomes are available. Here we review basic research in animal models of perinatal alcohol exposure to assess the potential of global environmental manipulations to ameliorate the neurobehavioral effects associated with FASD. Enhancement of the postnatal environment via neonatal handling, environmental enrichment, or rehabilitative or “therapeutic” motor training, can improve behavioral performance and ameliorate or even eliminate some deficits in perinatal alcohol-exposed rats and mice. While neuroanatomical changes associated with the behavioral improvements have been reported in some models, there generally appears to be a persistent impairment in neuronal plasticity. Such research suggests that it may be possible to manage the postnatal environment or experience of children with FASDs to improve function. It is, however, necessary to consider the difficulties in translating findings from research in animals to the clinic, school or home because sex-, postnatal age- and species-specific differences are critical factors in how specific environments may influence brain development. Continued study of the potential ameliorative effects of neonatal handling, environmental enrichment, and rehabilitative training as “therapies” in animal models will remain a valuable source of information for eventually devising treatments for children with FASDs.

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Keywords: Fetal alcohol syndrome (FAS); Alcohol-related neurodevelopmental disorders (ARND); Animal models; Environmental enrichment; Treatment (Therapy)

Contents

1. Introduction ........................................... 203
2. Neonatal handling .................................. 204
3. Environmental enrichment .......................... 206
4. Therapeutic or rehabilitative training ............... 207
5. Conclusions ........................................... 208
   Acknowledgements .................................. 209
   References ........................................... 209

*Corresponding author. Department of Obstetrics & Gynecology, Wayne State University, 275 East Hancock, Detroit, MI 48201, USA.
Tel.: 313 577 8671; fax: 313 577 8554.
E-mail address: j.hannigan@wayne.edu (J.H. Hannigan).
1. Introduction

Fetal alcohol spectrum disorders (FASDs) are a broad range of deleterious physical and functional outcomes associated with exposure to alcohol during gestation (Hannigan and Armani, 2000; Bertrand et al., 2004). The most severe FASD, fetal alcohol syndrome (FAS), was defined in the early 1970s as a pattern of pre- and/or postnatal growth restriction, facial dysmorphology, and mental retardation in infants born to alcoholic women (Jones and Smith, 1973). Based on 30 years of research, the cognitive deficits in children with FAS are now recognized to include persistent, dose-dependent patterns of specific dysfunctions even in the absence of mental retardation (e.g., Jacobson and Jacobson, 1994; Roebuck et al., 1999; Spohr, 1996; Streissguth et al., 1991; Streissguth et al., 1994).

There is considerable variability in the range and magnitude of prenatal alcohol-induced effects making definitive diagnoses of FAS often difficult. Reported incidence has varied from “0” in select populations (Abel, 1995), to 0.33 cases of FAS per 1000 live births (Abel and Sokol, 1991), between 1.3 and 4.6 per 1000 in the general population (Bertrand et al., 2004; Sampson et al., 1997), to as many as 60 per 1000 births to alcoholic women (Sampson et al., 1997). Estimates of the incidence of the whole range of FASDs are more difficult to determine (Bertrand et al., 2004; Stratton et al., 1996), although one estimate suggested that the combined prevalence of FAS and alcohol-related neurodevelopmental disorders (ARNDs) may be as high as 9.1 per 1000 in the general population (Sampson et al., 1997).

Much of the clinical and behavioral variability associated with FASDs may be attributed to differences in the frequency, pattern, and/or amount of alcohol consumption during pregnancy (Abel and Hannigan, 1995). A number of environmental factors associated with poverty, including undernutrition (cf., Beblo et al., 2005; Stark et al., 2005), increased stress, poor health, poor social or medical support, and a greater likelihood of exposure to environmental contaminants, may all contribute to susceptibility to alcohol’s teratogenic effects (Abel and Hannigan, 1995). Smoking, cocaine, and other drugs of abuse that can be part of any environment also play a role (e.g., Sood et al., 2005; Nordstrom Bailey et al., 2005) and these same factors appear to interact postnatally with, and may exacerbate, the life-long impact of prenatal alcohol exposure (Streissguth et al., 1996).

There is of course considerable interest in preventing FASDs. For example, pharmacological treatments such as naltrexone or serotonin 5-HT1A agonists for reducing alcohol craving, withdrawal symptoms, or other effects of alcohol on drinkers—who could include mothers—are being studied (e.g., Svikis and Reid-Quinones, 2003; Gillespie et al., 1997; Pilati et al., 1995). However, until FASDs can be prevented, there will be a continued critical need to treat children affected by in utero alcohol exposure. One way to limit, if not prevent FASDs, is to mitigate the life-long impact of prenatal alcohol exposure. Rather than treatments aimed at the pregnant mother, this review focuses on postnatal experimental manipulations targeted to offspring, expanding our previous discussion of this topic (Hannigan and Berman, 2000).

There are very few studies assessing amelioration of fetal alcohol effects on children or adults (cf., Morse and Weiner, 1996), and those are complicated by the substantial variability in the expression of FASDs (ICCFAS, 2000), and that the fact that there can be considerable similarities among children with different diagnoses along the FASD spectrum (Mattson and Riley, 1998, 1998, 2001; Roebuck et al., 1999). The establishment of specific treatments requires a clear understanding of who is being treated for what because a single effective treatment capable of targeting the whole range of neurobehavioral outcomes of the FASDs may not be found. Further, because considerable similarities exist among children with different diagnoses, it appears unlikely that differential diagnoses will be useful in addressing the neurobehavioral or cognitive problems of an individual child, or choosing treatments.

Psychotherapeutic drugs are often employed as specific treatments for developmental behavioral disorders (Gadow, 1986; Hannigan and Randall, 1996). This includes pharmacological treatments aimed at reducing alcohol withdrawal and its effects on the neonate (e.g., Thomas et al., 1997, 2001) or that may target specific mechanisms of alcohol teratogenesis (e.g., Thomas et al., 2000, 2004a, b; Heaton et al., 2000; Mitchell et al., 1999). While such medications do manipulate the “postnatal experience,” experimental studies of drug treatments of rats are beyond the scope of the current review. We note that there are also limitations to psychoactive drugs in treating the broad cognitive and developmental delays in FASD (cf., Hannigan and Randall, 1996; Hannigan and Berman, 2000). In contrast to the search for medications targeting specific behavioral problems, such as Ritalin® for hyperactivity, we describe effort to define more global, environmentally based treatment for FASDs.

This approach was inspired by examining the environmental circumstances (i.e., physical, social/familial and economic) of individuals with FASD. It is our premise that children with FASD are at greater developmental risk because they are raised in “at-risk” environments. Parent and advocacy groups have long recognized the importance of providing each child with a well-managed environment that optimizes favorable development and limits provocative features (e.g., Hinde, 1993; Kleinfeld, 2000; Lutke, 1993; Streissguth, 1997). Indeed, impoverished or poor postnatal environments may exacerbate the impact of prenatal alcohol exposure, making exposed children more susceptible to developing so-called “secondary disabilities” such as substance abuse, inappropriate sexual behavior, and trouble with the law (Streissguth et al., 1996). Conversely, raising children under appropriately

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structured, enriched conditions can reduce this risk and substantially improve outcomes. For example, two of the most potent protective factors against developing postnatal secondary disabilities included a stable, nurturing household—which might include foster care—and a “good quality home” environment between 8 and 12 years of age (Streissguth et al., 1996). Here we review three experimental manipulations of postnatal environment and experience used to “treat” fetal alcohol effects in animal models: early or neonatal handling, environmental enrichment, and rehabilitative motor training.

2. Neonatal handling

Neonatal handling is a well-characterized experimental procedure that produces long-lasting alterations in behavior, learning, and neuroendocrine function in rats and mice, particularly in later responses to challenging or stressful stimuli (e.g., Ader, 1968; Denenberg, 1964; Denenberg et al., 1968; Levine, 1957, 2005, 1967; Levine et al., 1967). Basic neonatal handling is a brief (3–15 min) daily separation of pups from the dam and/or from each other (e.g., Camp et al., 1984; DeNelsky and Denenberg, 1967; Meaney et al., 1991). This often includes “gentling” the animals during the separation (e.g., Ader, 1968; Clausing et al., 1997). This seemingly innocuous procedure improves post-weaning learning, facilitates maturation, and modifies neuroendocrine responses to stressful stimuli in normal animals (Clausing et al., 2000). Key factors that modify the effectiveness of the pre-weaning manipulation include species, strain and sex of the animals, several timing variables (i.e., age at start; duration of handling in number of days and min/day; interval between handling and testing; age at testing, etc.), whether the pups are housed individually or as a litter during separation from the dam, aspects of maternal behavior upon return of the pups as a litter to the dam (e.g., the dams’ competency in pup retrieval), and the nature of the neurobehavioral outcome assessed. Early handling should be contrasted with maternal deprivation experiments that use longer periods of separation of dams and litters (i.e., hours to days), and often have deleterious effects on pup development (cf., Levine, 2005).

Effects of neonatal handling are largely mediated by changes in responsiveness of the hypothalamic pituitary–adrenal axis (HPA) to stress (Hess et al., 1969; Levine, 1967, 2005; Levine et al., 1967; Meaney et al., 1996). For example, rats handled during the neonatal period have a blunted peak corticosterone response and a faster return to baseline when exposed to a stressor in adulthood (Meaney et al., 1991). Other manipulations in the early postnatal period that are not expressly defined as handling (e.g., pre-weaning learning trials) have sometimes produced similar results as handling. For example, Clausing (2000) has used “communal rearing,” where two dams and their litters are housed together and weaning is delayed until PN28, to study the effects of the preweaning environment on prenatal alcohol effects, and argues that it is a more naturalistic and clinically relevant manipulation (Mothes et al., 1996). An excellent review by Clausing et al. (2000) details the importance of several factors in neonatal handling, and outlines its’ role in the modification of fetal alcohol effects.

One of the very earliest studies of fetal alcohol effects in an animal model included neonatal handling as a variable (Gallo and Weinberg, 1982; Weinberg and Gallo, 1982). The goal was not to test handling as a treatment per se, but to control explicitly for non-specific effects associated with handling during the measurement of neurodevelopmental milestones (e.g., body weight; age at eye opening, etc.). However, the effects of this neonatal handling during development were dramatic. Neonatal handling completely eliminated passive avoidance learning deficits (Gallo and Weinberg, 1982), and attenuated endocrine deficits in female rats (Weinberg and Gallo, 1982). Despite these early studies, it is remarkable, as noted by Clausing et al. (2000), that the number of studies on the interactions between handling and the neurobehavioral effects of prenatal drug exposure is “surprisingly small.” In the last 5 years, however, more research has been done in this area.

As far as we are aware, the first time a “classical” neonatal handling regime was expressly employed as a treatment after prenatal alcohol exposure was the study by Weinberg et al. (1995). Here several sex-specific interactions of prenatal exposure and neonatal handling were shown after a 3-min separation of individual rat pups from the dam and litter each day from PN2 to PN15. Prenatal alcohol-exposed males, but not females, showed an exaggerated hypothermia response after an acute ethanol challenge (2.0 g/kg) at PN70, an effect that was eliminated by neonatal handling. Later, Gabriel and Weinberg (2001) studied the effects of prenatal alcohol and subsequent handling on both consummatory behavior and conditioned taste aversion tested under water-deprived and non-water-deprived conditions. They found that the amount of a novel flavored saccharin solution that rats drank was increased independently by both prenatal alcohol exposure and neonatal handling, results that were interpreted as decreases in an initial neophobia. It was also reported that neonatal handling significantly increased the magnitude of a conditioned saccharin taste aversion compared to non-handled animals, but this effect of handling was not evident in alcohol-exposed offspring. These results suggested that neonatal handling may not be effective in ameliorating all of the deficits in these animals exposed prenatally to alcohol (Gabriel and Weinberg, 2001).

The results of studies assessing whether neonatal handling can ameliorate deficits in spatial learning tasks after prenatal exposure to alcohol have been inconsistent. For example, Lee and Rabe (1999) found that prenatal alcohol exposure produced profound deficits in a T-maze reversal task in young male and female offspring, although initial learning was unimpaired. Importantly, this alcohol-induced deficit was completely eliminated by neonatal
Prenatal alcohol or aging on spatial memory (Gabriel et al., 2002). Prenatal alcohol produced small increases in the latency to find the platform and abnormal search patterns only at PN60, and if anything, neonatal handling reduced escape latencies in controls but not in prenatal alcohol-exposed animals. No significant effects of either prenatal alcohol or handling were seen in older animals. The conclusion from these experiments was that neonatal handling did not ameliorate effects of either prenatal alcohol or aging on spatial memory (Gabriel et al., 2002).

Other early manipulations such as the delayed weaning and communal rearing procedures mentioned above have also yielded inconsistent results. Although communal rearing was effective in reversing prenatal alcohol-induced deficits in a conditioned taste aversion task, there was no clear benefit on radial arm maze performance (Opitz et al., 1997) or on motor behavior (e.g., rearing, locomotion; Mothes et al., 1996). In contrast to delayed weaning, Zimmerberg and Weston (2002) found that premature weaning on PN15 had a significant negative impact on somatic growth and spatial learning deficits in a Morris maze, but not on locomotor activity (Zimmerberg and Weston, 2002). Considered together with the results of Gabriel et al. (2002) who found no benefit of neonatal handling on Morris maze performance, these results suggest that spatial learning may not be improved, or may even be made worse, by manipulations that compromise the quality of the early postnatal environment. Unpublished data from our lab using a prenatal binge alcohol exposure paradigm from GD8 to GD20 and handling procedures identical to those used by Dr. Weinberg’s lab also suggest that neonatal handling may exacerbate performance deficits in the Morris maze. It is worth noting that some varieties of neonatal handling (e.g., prolonged isolation or when hypothermia is permitted) can be stressful (cf., Levine, 2005; Meaney et al., 1991, 1996).

Later studies have elaborated on the reports by Weinberg and colleagues in the early 1980s. Specifically, Weinberg et al. (1995) reported that early handling eliminated the preweaning weight deficit in prenatal alcohol-exposed rats, as well as the exaggerated hypothermia following an ethanol challenge. Neonatal handling also eliminated the increased plasma corticosterone response to restraint stress in prenatal alcohol-exposed females (males were not tested). However, neonatal handling increased the corticosterone response to an ethanol challenge in both males and females, so not all of the effects of neonatal handling can necessarily be considered to be beneficial. In addition, plasma corticosterone levels which were elevated immediately after a water-deprived condition aversion test were reduced by neonatal handling in all groups with no interaction with prenatal alcohol exposure (Gabriel and Weinberg, 2001). Finally, plasma corticosterone levels assessed immediately after the last trial of a Morris maze test were higher in prenatal alcohol-exposed animals than in non-exposed animals, but there were no significant effects or interactions due to neonatal handling (Gabriel et al., 2002). Again, some but not all effects of prenatal alcohol exposure can be modified by neonatal handling.

The interactions between prenatal alcohol exposure (via inhalation) and postnatal handling on endocrine responses were also assessed in rats by Ogilvie and Rivier (1997). Pups were handled 15 min/day for 3 weeks and on PN22 corticosterone and ACTH were assessed before, during and after a foot shock stressor. Prenatal alcohol exposure alone significantly increased and neonatal handling alone marginally reduced ACTH levels during the shock. However, unexpectedly, alcohol-exposed offspring that were also handled showed even higher ACTH release during shock, an effect moderated by sex and that was not dependent on whether or not the litters had been cross-fostered (Ogilvie and Rivier, 1997). Briefly, the greater increases in ACTH levels were seen in females regardless of fostering, and in fostered males. For corticosterone, plasma levels in males measured during the shock were significantly reduced by neonatal handling compared to the alcohol-exposed, non-handled group. It should be noted that Clausing et al. (2000) argued that interpretation of prenatal alcohol effects on HPA axis efficiency cannot be supported by data collected at time points “optimized for ACTH” and not for corticosterone, even though there are clearly complex interactions between prenatal alcohol exposure and postnatal experience on regulation of HPA axis responses to stress.

The apparent lack of responsiveness of HPA function to neonatal handling after prenatal alcohol was examined at a different level by assessing the expression of corticotropin-releasing factor (CRF) mRNA in the paraventricular nucleus by in situ hybridization (Gabriel et al., 2005). Prenatal alcohol exposure elevated CRF mRNA levels compared to untreated controls, and a significant sex-handling interaction due to higher CRF mRNA levels in non-handled males than in non-handled females was also evident. This sex difference was not present in the handled groups because handling significantly reduced CRF mRNA levels in the males. Further, there were no significant interactions between prenatal alcohol exposure and neonatal handling, although in a follow-up analysis of a subset of the values from males only, there were marginal reductions in CRF mRNA due to neonatal handling in the control groups (p’s = 0.06–0.07), but not in the alcohol-exposed males. The authors concluded that prenatal alcohol exposure elevates basal CRF mRNA levels. Neonatal handling alters those levels in a sex-dependent manner, but the handling is ineffective in ameliorating those increases due to alcohol-exposure itself (Gabriel et al., 2005). While these studies of both behavioral and endocrine outcomes are fairly consistent in showing significant interactions between prenatal alcohol exposure and neonatal handling, the effects of handling are clearly not always in a beneficial direction.
3. Environmental enrichment

Research with environmental enrichment in rodents typically entails increased social interaction with conspecifics, more variety and variability in sensory experience—or increased “stimulus complexity”—greater and more varied locomotor activity, and sometimes learning specific training activities (Greenough, 1976; Rosenzweig, 1996). Rearing animals in enriched or complex environments stimulates CNS development, facilitates recovery of CNS function, and can enhance behavioral performance (Dong and Greenough, 2004; Greenough, 1976; Rosenzweig, 1996; Will et al., 2004). We and others have studied the potential “treatment effectiveness” of postweaning environmental enrichment on specific structural and functional fetal alcohol effects in rats and mice assessing the hypothesis that enriching the postnatal environment would ameliorate fetal alcohol effects (Hannigan et al., 1993; Berman et al., 1996; Berman and Hannigan, 2000; Hannigan and Berman, 2000; Wainwright et al., 1993).

Several reports have now demonstrated that rearing rats in an enriched environment after prenatal alcohol exposure can mitigate fetal alcohol effects on behavior (e.g., Clausing et al., 2000; Hannigan et al., 1993; Klintsova et al., 2000; Mothes et al., 1996; Wainwright et al., 1993). In our work, male and female offspring of pregnant rats exposed to high “binge” levels of alcohol from gestation day 8 (GD8) through GD20, and pups from untreated controls, were either housed for 8 or more weeks in enriched environments consisting of same-sex groups of ~12 rats in large arenas filled with various objects that the animals could play on, manipulate, chew, and crawl into. Control groups of rats were housed in isolation in steel/wire cages. Beginning at PN63, hind limb gait and spatial learning in a Morris water maze were assessed. Relative to non-exposed groups, rats exposed prenatally to alcohol and raised in isolation had locomotor gait dysmetrias indicative of a functional “ataxia.” After environmental enrichment, there were no differences in hind limb gait in the control groups relative to controls reared in isolation, and importantly there was no longer any evidence of ataxia in the prenatal alcohol-exposed group. Some unspecified aspect(s) of the “experiential complexity” of the enrichment procedures—that is, the sensory, motor and/or social components—had eliminated functional fetal alcohol effects on motor behavior (Hannigan et al., 1993).

Spatial learning deficits in a Morris maze were also affected by the postnatal rearing environment. Specifically, rats exposed prenatally to alcohol and reared in isolation showed learning deficits during “reversal learning” when the escape platform was shifted to a new position after 4 days of training at the original platform location (Hannigan et al., 1993; Hannigan and Berman, 2000). In all prenatal treatment groups, environmental enrichment substantially decreased escape latency during the initial task acquisition, as well as during the reversal phase, demonstrating improved learning (Hannigan et al., 1993). Other data from our lab suggest that the effects of postweaning environmental enrichment are persistent, regardless of prenatal alcohol exposure (O’Leary et al., 2002). In this study, rats raised after weaning for 6 weeks in enriched, social or isolated environments were then returned to standard housing conditions (same-sex, groups of three) for 6 weeks and then tested for spatial learning in the Morris maze ~PN108. The enriched rats showed improved Morris maze performance regardless of prenatal alcohol exposure compared to rats housed in isolated or social conditions. These results are similar to our earlier study that found that enrichment improved spatial learning when rats were trained and tested immediately after the end of enrichment at PN63 (Hannigan et al., 1993). Those beneficial effects of enrichment that were evident immediately after enrichment persisted for weeks until ~PN108 (O’Leary et al., 2002), an encouraging finding regarding the possible effectiveness of postnatal treatments for fetal alcohol effects. These results are very similar to the reduced spatial learning deficits reported in mice after enrichment (Wainwright et al., 1993), and demonstrate that environmental enrichment can improve learning in a task reflective of the spatial learning deficits seen in FASD (e.g., Uecker and Nadel, 1996, 1998). Because the beneficial effects of environmental enrichment on prenatal alcohol deficits are likely to be mediated by the same neural processes underlying learning and memory (cf., Rosenzweig, 1996), it is important to note that these results also indicate that even offspring whose cognitive abilities may be compromised by prenatal alcohol exposure may still benefit from global postnatal, post-weaning environmental “treatments” designed to promote neurobehavioral plasticity.

Structural alterations in the brain are another key response to environmental enrichment, with enriched animals consistently having more complex neuropil, increased dendritic branching, and more synapses and neurotransmitter receptors compared to their non-enriched counterparts (e.g., Mohammed et al., 1993; Young et al., 1999; Williams et al., 2001). Wainwright et al. (1993) measured neocortical thickness in mice exposed prenatally to alcohol via liquid diet and found that postweaning environmental enrichment did not reverse prenatal alcohol-induced decreases in neocortical thickness. Based on enhanced spatial learning responses to enrichment (Wainwright et al., 1993; Hannigan et al., 1993), and the documented sensitivity of the hippocampus to prenatal alcohol exposure (Barnes and Walker, 1981; Ferrer et al., 1988; Krahl and Berman, 1996; Krahl et al., 1999; West et al., 1988), we hypothesized that the morphology of neurons in the hippocampus in prenatal alcohol-exposed animals would also be responsive to environmental enrichment (Fiala et al., 1978; Greenough, 1976; Juraska et al., 1989), possibly mediating the behavioral improvements in spatial learning. This was tested by assessing dendritic spine density on terminal tertiary apical and basilar dendrites of pyramidal neurons in CA1 and CA3 of the hippocampus from rats exposed prenatally to alcohol and then reared in
an enriched environment for 6–8 weeks after weaning. As expected, environmental enrichment indeed produced sex-influenced increases in apical and basilar dendritic spine density in hippocampus of alcohol-naive animals. However, environmental enrichment did not produce significant changes in the hippocampal spine density of rats exposed prenatally to alcohol (Berman et al., 1996; Berman and Hannigan, 2000). Contrary to our hypothesis, these results suggest that prenatal alcohol exposure compromises the ability of the hippocampus to increase spine density in response to the environmental enrichment. Indeed, neither the parietal cortex nor the hippocampus appear to respond normally to environmental enrichment. The lack of synaptic plasticity is consistent with a reduced reactive axonal sprouting in olfactory tubercle of prenatal alcohol-exposed animals after olfactory bulbectomy (Gottesfield et al., 1989), but may be in contrast to the prenatal-alcohol induced increase in entorhinal lesion-induced heterotopic sprouting in hippocampus (Dewey and West, 1984; West et al., 1984). Altered hippocampal synaptic plasticity after prenatal alcohol exposure is also evident in reduced LTP and related electrophysiological measures, as we have reviewed previously (Krahl and Berman, 1996).

These results imply that a basic mechanism thought to underlie synaptic plasticity in the hippocampus—that is increased postsynaptic spine density—in response to environmental enrichment may be compromised; but since motor performance and learning were improved after postweaning enrichment, the CNS of the prenatal alcohol-exposed rats apparently retains sufficient plasticity, somewhere, or by some alternative mechanism, to benefit from environmental stimulation. One possibility is that the beneficial effects of environmental enrichment on behavior may be mediated by neural plasticity in CNS areas other than hippocampus (Berman and Hannigan, 2000) or parietal cortex (unpublished findings). Alternatively, because the passive exposure to environmental enrichment failed to produce structural change in hippocampus (Berman et al., 1996), it may be that the learning environment (cf., Greenough, 1976; Rosenzweig, 1996), did not sufficiently engage hippocampus for the prenatal alcohol-exposed rats, and not necessarily that the hippocampus was insensitive to enrichment. The discovery of neurogenesis in the adult hippocampus (Kempermann et al., 2004; van Praag et al., 2000) that is stimulated by environmental enrichment suggests other interesting hypotheses about the role of the postnatal environment in ameliorating fetal alcohol effects.

These results also raise questions concerning the mechanisms of neural plasticity and why they are impaired in hippocampus, which brain systems still retain neuroplasticity, and through which mechanism amelioration occurs after prenatal alcohol. Findings answers to these questions is important because they could lead to intervention strategies that may circumvent prenatal alcohol’s enduring effects on neural plasticity (Krahl and Berman, 1996) and behavior (cf., Heaton et al., 2000; Lewis, 2004; Saunders et al., 1995; Pinaud, 2004; Torasdotter et al., 1996).

4. Therapeutic or rehabilitative training

The neonatal handling and enrichment work focused on rodent models of prenatal alcohol exposure and the effect of early neonatal alcohol exposure targeting the “brain growth spurt”—or the third-trimester equivalent of brain development in the rat (cf., Dobbing and Sands, 1979)—may be differentially sensitive to environmental treatments. It is also not yet known if there are brain region-specific postnatal “critical periods” for environmental manipulations to ameliorate the effects of perinatal alcohol exposure (cf., Fiala et al., 1978). Some of these questions have been addressed by the work of Klintsova et al. using early neonatal alcohol administration during the “brain growth spurt,” an exposure which produces a permanent loss of Purkinje cells (Bonthius and West, 1991; Napper and West, 1995). Klintsova et al. (1997, 1998, 2000) have assessed the ameliorative effects of complex motor learning—or rehabilitative training—on the enduring impact of perinatal alcohol exposure on cerebellar-dependent behavior and anatomy. “Rehabilitative training” or therapeutic training refers to a sequence of forced learning complex motor skills (Klintsova et al., 1998, 2002). In contrast to typical enrichment procedures, where animals experience the varied sensory, motor and social interactions associated with the environment in an unstructured way, “forced” training procedures of Klintsova et al. (1998, 2002) were designed to focus on learning a specified sequence of complex motor tasks, ensuring engagement of cerebellar motor circuitry and allowing for a more precise localization of synaptic plasticity thought to support motor learning. This work minimizes or eliminates difficulties raised by the possibility that rats in the various alcohol treatment groups interact differently with the enriched or “training” environment, and therefore have unequal enrichment experiences. Finally, whereas earlier enrichment studies examined the cortex and hippocampus, Klintsova and colleagues focused on cerebellar-dependent behaviors and anatomy because their neonatal alcohol exposure period (i.e., PN4–PN10) included the stage at which the developing cerebellum is extremely sensitive to the damaging effects of alcohol.

In these studies, rats exposed to neonatal alcohol via intragastric intubation began complex motor training ~PN180. This training consisted of learning to negotiate an “obstacle course” in which the rats climbed ropes, chains and rods, traversed narrow bridges, beams and ladders, etc over several days. Even though alcohol-exposed groups took more trials than controls to reach a learning criterion, training continued until all animals learned the complex motor sequence. Following this training, the motor performance of these animals was assessed on a variety of tasks (Klintsova et al., 1998).
including traversing parallel bars where the distance between the bars increased over trials, a task particularly sensitive to the poor hind limb coordination seen in alcohol-affected rats (e.g., Hannigan and Riley, 1988; Thomas et al., 2004a). As expected, animals exposed to alcohol during the neonatal period slipped from the bars significantly more often than non-exposed control animals. However, after rehabilitative training, motor coordination and balance in the neonatal alcohol-exposed rats improved to a point where they were not significantly different from controls (Klintsova et al., 2000). Further, Klintsova et al. (1998) found that it is the learning in this complex motor task that is required for the generalized benefit since forced motor activity alone without a learning component, such as walking in a treadmill, was ineffective in improving performance or influencing cerebellar physiology or anatomy (Klintsova et al., 1998).

Klintsova and colleagues also showed that early postnatal alcohol exposure significantly reduced the density of molecular layer Purkinje cells compared to unexposed controls by up to 20% (Klintsova et al., 2000) but that the numbers of synapses on Purkinje cells were increased after rehabilitative training in adult rats after neonatal alcohol exposure (Klintsova et al., 1997, 2000). There were also significantly more parallel fiber synapses per Purkinje neuron in trained than in untrained groups, regardless of alcohol exposure. This study demonstrated that adult rat cerebellar neurons surviving alcohol exposure during the neonatal period continue to exhibit significant plasticity by responding to rehabilitative training begun in adulthood. Taken together, these results suggest that postnatal environment and experience modifies perinatal alcohol-induced changes in the rat brain, and that the effectiveness of the ameliorative or rehabilitative experience may be either regionally specific (i.e., occurring in hippocampus, cerebellum, and/or neocortex) and/or variably expressed. That is, cerebellum appears to be capable of significant modification even in adulthood, where the hippocampus may not (cf., Fiala et al., 1978).

In summary, the work of Klintsova et al. demonstrated that training on complex motor tasks, with attainment of consistent learning criteria—and not exercise alone—ameliorates the motor and learning deficits and effects in the cerebellum resulting from neonatal alcohol exposure during the “brain growth spurt” in rats. Importantly, the work by Klintsova et al. also demonstrated that rehabilitative training works even in adulthood.

5. Conclusions

Fetal alcohol spectrum disorders (FASDs) are characterized by life-long problems in growth, behavior and cognition (e.g., Bertrand et al., 2004; Stratton et al., 1996). The behavioral effects, paralleled in animal models (Hannigan, 1996), imply that dysfunctional mechanisms of neuronal plasticity contribute substantially to the FASDs. The research reviewed here demonstrates that modification of the rodent offspring’s postnatal experience, by neonatal handling, environmental enrichment, or rehabilitative training, can improve behavioral performance and ameliorate or even eliminate some deficits seen with prenatal alcohol exposure. Which specific components of that experience, such as motor activity, social interactions, or activation of the HPA axis and/or other neural system, are necessary or sufficient to affect behavioral outcomes have yet to be determined.

Some but not all postnatal manipulations appear to be able to ameliorate specific neuroanatomical or neuroendocrine effects of perinatal alcohol exposure. Despite the functional effectiveness of enrichment, a persistent impairment in neuronal plasticity remains in hippocampus, evidenced by a failure of hippocampal pyramidal neurons to show increases in dendritic spine densities in rats exposed prenatally to alcohol (Berman et al., 1996), and in neocortex, assessed as increases in cortical thickness in mice (Wainwright et al., 1993). The reasons for this poor neural response to environmental enrichment in some CNS areas also remain to be determined. Similarly, rehabilitative training has been effective in improving behavior and some neuroanatomical measures in cerebellum (Klintsova et al., 1997, 2002). Possible reasons for differences among the neonatal handling, environmental enrichment and rehabilitative training studies are many, including differences in the periods and patterns of alcohol administration, the nature of the intervention, when during maturation the intervention occurs, brain-region specific sensitivity to alcohol and/or environmental interventions, and the type of testing used to assess cognitive and motor functions. The effectiveness of neonatal handling in ameliorating the effects of prenatal alcohol exposure is also mixed in terms of which outcomes may be improved (e.g., somatic growth versus simple learning) or not (e.g., reactivity to particular stressors). The dissociations between behavioral and neuroanatomical outcomes with enrichment and rehabilitation are mirrored in the inconsistencies between behavioral and endocrine outcomes following neonatal handling.

In summary, we have reviewed evidence that the expression of these fetal alcohol effects is influenced by the quality of the environments in which the animals are reared, and that there can be beneficial effects of neonatal handling, environmental enrichment and rehabilitative training. The results point optimistically towards the eventual development of effective postnatal environmental/experiential treatment strategies for children with FASDs. However, it is important to consider that the application of findings from animal studies may not translate in any simple or straightforward manner to interventions in the clinic, school or home. Analogous handling, enrichment or complex motor training might not translate into effective environmental “therapies” or rehabilitation for children. For example, there are case-reports and anecdotal information suggesting that children with FASDs may respond poorly to
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References


