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What Research with Animals Is Telling Us about Alcohol-Related Neurodevelopmental Disorder

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HANNIGAN, J. H. *What research with animals is telling us about alcohol-related neurodevelopmental disorder.* PHARMACOL BIOCHEM BEHAV **55**(4) 489–499, 1996.—The substantial advances in understanding fetal alcohol syndrome over the past 20 years were made in large part because of research with animals. This review illustrates recent progress in animal research by focusing primarily on the central nervous system effects of prenatal alcohol exposure. Current findings suggest further progress in understanding consequences, risk factors, mechanisms, prevention and treatment will depend on continued research with animals. **Copyright © 1996 Elsevier Science Inc.**

Fetal alcohol syndrome (FAS)   Animal models   Neurobehavioral teratology

THE designation of a pattern of growth retardation, facial anomalies and mental retardation in infants born to alcoholic women as fetal alcohol syndrome (FAS) in the early 1970s (92) was the first time a teratogenic outcome was named for the agent thought to cause the abnormalities (2). Researchers began developing animal models to address initial skepticism that maternal alcohol consumption during pregnancy could have such devastating effects on infants (27). Animal models of alcohol-related birth defects (ARBDs) and the recently defined alcohol-related neurodevelopmental disorder (ARNDs) (173) have done that and have advanced our understanding of the pathology (50), risk factors and biological mechanisms of FAS and ARNDs (5).

Animal models confer distinct advantages on the study of how alcohol acts on fetuses, how other influences associated with alcoholism in people (e.g., codrug abuse or poor nutrition) contribute to fetal alcohol effects and perhaps how FAS might be treated or prevented (173). We have recently reviewed these advantages, certain disadvantages and some practical and analytical issues in the design and use of animal models (75). In humans, alcohol interacts with several genetic, ontogenetic, experiential, social and behavioral factors and does so on many levels (e.g., pharmacological, biochemical, physiological). In animals, many of these issues can be simplified because experiments are conducted under controlled circumstances with perhaps hundreds of subjects, and the potent factors that may be confounded with the impact of alcohol are controlled, excluded and/or measured. This control greatly enhances the sensitivity of studies.

The advantages of simplification and experimental control are balanced by other difficulties and limitations inherent to animal models (75,185). It is important to remember that there is no single ideal animal model of ARNDs. There is also no animal model of FAS per se because offspring of pregnant animals given alcohol do not display all the clinical signs found in people. However, significant advances are being made by using well-defined animal models that can be valid and effective tools for examining specific outcomes or mechanisms of FAS. This article reviews recent progress with animal models for understanding primarily central nervous system (CNS) effects in FAS, particularly ARNDs.

OUTCOMES IN ANIMAL MODELS CAN PREDICT THOSE IN HUMANS

The biological and neurobehavioral sequelae of prenatal alcohol exposure in animals remain remarkably consonant with clinical effects in humans (50), which has helped validate the animal models, specify that particular clinical outcomes are due to alcohol per se and indicate other problems that may be found in humans (3,12,81,117,140). For example, auditory processing deficits (31,32) and renal anomalies first described in animals (144) led to later identification in FAS children (34,43,44,181). In general, animal models confirm that the life-long sequelae of prenatal alcohol exposure include poor somatic growth, major organ malformation, craniofacial anomalies and associated CNS dysfunction (150). CNS dysfunction is expressed as a reduced capacity for basic adaptive functioning, including impaired neural plasticity, poor learning and/or abnormal responses to challenging situations. We cannot predict what other outcomes in rodents may prove particularly fruitful in understanding humans, but there are many candidates.

FETAL ALCOHOL EFFECTS ARE DOSE DEPENDENT

Accurately determining threshold doses for different prenatal alcohol-related outcomes (90) continues to be a critical research area in animal models. Although the total absolute amount of alcohol consumed (dose) and the pattern of alcohol drinking (e.g., binging) are both critical factors (19,197), controlled experiments have clearly demonstrated that the peak maternal blood alcohol level (BAL) is the most important determinant of the likelihood and magnitude of ARNDs in offspring (198,199). The assumptions about alcohol absorption, metabolism or pharmacodynamics sometimes made in epidemiological studies (5) need not be made in animal studies, which can precisely control alcohol dose and exposure pattern and measure actual BALs (75,183). Thresholds for particular outcomes remain to be determined.

FETAL ALCOHOL EFFECTS DEPEND ON WHEN ALCOHOL EXPOSURE OCCURS

Animal models have demonstrated that ARNDs are determined in part by when peak BALs occur during pregnancy, which is defined as so-called critical periods. For example, early embryonic alcohol exposure in mice or monkeys is associated with facial dysmorphology (36,178). The CNS appears to be sensitive to deleterious effects of alcohol throughout perinatal development (38,39,198) and different cell types within the CNS appear sensitive to alcohol at certain stages (21,25,41) or even on single days (25,139). Prenatal and/or neonatal alcohol exposure will disrupt individual brain areas, depending on neuronal cell cycle and when neuron populations proliferate, migrate and differentiate (122–124,133). For example, neonatal alcohol exposure during cerebellar Purkinje cell differentiation caused significant Purkinje cell loss (107) and reduced expression of cerebellar myelin basic protein mRNA levels (206). In contrast, dose-equivalent prenatal alcohol exposure during Purkinje cell neurogenesis did not affect these measures (107,206). Animal models can account for species differences in gestational course. For example, by administering alcohol to neonatal rats between postnatal days (PN) 4 and PN10, the CNS developmental equivalent of the third trimester of gestation in humans, this neonatal period in rats effectively models late gestational alcohol exposure (197). Animal research is showing that the times before and after pregnancy are also critical periods for alcohol exposure. Paternal (4,35) and maternal alcohol consumption, even when it occurs before pregnancy (100,182), and alcohol consumption by lactating mothers (177) can influence outcome in offspring.

RETARDED GROWTH AND PHYSICAL ABNORMALITIES ARE CONSISTENT OUTCOMES IN ANIMALS

Perhaps the most reliably demonstrated of the diagnostic criteria for FAS in animals is a dose-dependent reduction in fetal growth or birth weight (76). Low birth weight in people can be caused by many prenatal insults, so the systematic occurrence of growth retardation in animal models is evidence that alcohol per se retards development.

In all animal species assessed, dysmorphic patterns of facial features appear to resemble those in FAS children (1,8,58,169) and to occur when there were high BALs early in embryonic development (25,96). The regional selectivity of alcohol-induced CNS malformations is evident in children with FAS and in animal models. Derivatives of the neural crest, for example, appear to be particularly sensitive to early exposures (24,25,41,96), including the face and eyes. The distinctive craniofacial dysmorphology is also important because it is closely associated with CNS malformations (165). There was a positive association between craniofacial anomalies and holoprosenscephalic features in monkeys exposed to alcohol in utero (164).

Alcohol delayed the maturation of craniofacial areas in mouse embryos (59), and exposure at different days during gestation had specific teratogenic effects on the face caused by excessive cell loss along the rim of the anterior neural fold (97). Mice are keenly sensitive to the patterns of midface hypoplasia and short palpebral fissures (96), features seen also in monkeys (9,36) and detected radiographically in rats (56). Alcohol exposure after closure of the anterior neuropore did not have as profound an affect on the facial anlage (97). Alcohol's particularly selective toxic effects on cultured early embryonic neural crest cells in mouse (41) and in chick (25) may also play a role in facial anomalies.

NEUROANATOMICAL SEQUELAE ARE REGION SPECIFIC AND PROBABLY RELATED TO SPECIFIC DYSFUNCTIONS

Depending on age of exposure, rodent cerebellum, hippocampus and neocortex are all very sensitive to prenatal alcohol exposure (122,198). The alcohol-induced dysmorphology in each area reflects which cells are proliferating and differentiating. For example, Purkinje and pyramidal cells are more affected by prenatal exposure and granule cells by neonatal exposure to alcohol (198). In addition, CNS sensory systems also appear particularly affected by prenatal alcohol (125). Prenatal alcohol decreased olfactory bulb volume in rats (10) and neonatal exposure permanently reduced cell populations in rat olfactory bulb (17; cf. 18). Such changes could underlie functional deficits in sex-influenced scentmarking behavior (71) or food choice (115) and contribute to apparent deficits in learning about odors (10). Altered responses to odor cues may also mediate poor feeding behavior or maternal–infant interaction of FAS children (116). Auditory dysfunction associated with FAS (31) may be due to an early embryonic insult on the otic placodes expressed as excessive loss of neural progenitor cells (96,97). There is a high correlation between auditory dysfunction and anomalies of the eyes in FAS children (24). Prenatal alcohol exposure reduced the number of axons in rat (176) and mouse (7,135) optic nerve by 25–33% and the proportion of myelinated axons by 44% (7). Because no concomitant changes were apparent in the lateral geniculate nucleus or superior colliculus (7) and no alcohol effects on optic primordia in cultured rat embryos (59), optic nerve changes may reflect direct effects on retina late in gestation (176).

One implication of identifying sensory dysfunction in young FAS children is that relatively simple prosthetic devises (e.g., hearing aids or corrective lenses) and/or teaching strategies could facilitate information processing, cognitive development and general functioning in children with FAS/ARBDs (196).

BIOCHEMICAL AND NEUROCHEMICAL DYSFUNCTIONS ARE WIDE RANGING

Prenatal alcohol exposure disrupts mitochondrial function and protein synthesis (119,131,167,168), produces global decreases in enzymatic activity in rat brain (137) and reduces hepatic mitochondrial cytochrome oxidase activity by half in chick embryos (155). Glucose uptake into fetal neurons dissociated from alcohol-exposed brains was less than half that of unexposed neurons and was apparently related to a 50% decrease in expression of glucose transporter mRNA (166). Glucose utilization in cultured whole rat embryos was also reduced by alcohol (167). Alcohol may retard growth and delay maturation by inhibiting the synthesis of polyamines (e.g., putrescine) by ornithine decarboxylase (160).

The teratogenic actions of alcohol on CNS may also be mediated by direct actions on so-called ethanol-responsive genes such as tyrosine hydroxylase (62) and modulators of G-proteins (121). Gene regulation by alcohol can explain alterations in protein synthesis and calcium regulation. Calcium (Ca^{++}) plays an important role in many signal transduction processes, and dysregulation of Ca^{++}-dependent processes at any or all developmental stages may mediate cellular mechanisms of alcohol teratogenesis.

Alcohol enhances several indices of growth of primary cultures of rat cerebellar neurons (207). Leach et al. (99) showed that maturation of cultured preimplantation blastocyst stage whole mouse embryos was accelerated by alcohol. Alcohol stimulated hatching from zona pellucida, accelerated mitosis and increased morulae cavitation rates, apparently by enhancing intracellular Ca^{++} release and Ca^{++} uptake (99). These changes appear related to concentration-dependent surges in the intracellular release of Ca^{++} (170) and can be reversed by Ca^{++} chelators. Stachecki et al. (171) assessed the impact of such early embryonic alcohol-induced shifts in Ca^{++} levels by reimplanting mouse embryos exposed to alcohol in vitro into uteri of pseudopregnant mouse dams. Implantation and survival rates were increased in fetuses exposed to alcohol in vitro, although it is not known what processes are involved.

Neurotransmitters, hormones, growth factors and intracellular signal transduction are altered by alcohol exposure in utero (51,132), although generalizations are hard to make. Despite considerable differences in how alcohol was administered and when and where in the brain measurements were made, perinatal alcohol in animals often affected serotonin, dopamine, acetylcholine, glutamate and γ-aminobutyric acid (GABA) neurotransmitter systems (51). Many neurochemical outcomes do not appear to persist, and the behavioral sequelae thought to be mediated by these changes (e.g., dopamine and hyperactivity) often have developmental courses different from the neurochemical outcomes (51,80,117). Although there are enduring behavioral (117) and neurochemical (51,161,162) outcomes, this ontogenetic discordance emphasizes the difficulties in attributing cause and in devising pharmacological treatments (78).

The nature of neurotransmitter dysfunction may depend on when alcohol exposure occurs. For example, early embryonic alcohol exposure in chicks shifted the phenotypic expression of neuroblasts from cholinergic to GABAergic neurons (94). Glutamate function (particularly NMDA receptors) in the fetal brain may be more sensitive to alcohol than glutamate function in the adult brain (157). Ethanol depressed K^{+}-stimulated release of glutamate from fetal but not adult guinea pig hippocampus and immature fetuses were more sensitive to this effect than were mature fetuses (149). Ethanol inhibited NMDA receptor-mediated excitoxicity in cultured fetal neuronal cells (26), and prenatal alcohol decreased NMDA receptor-mediated Ca^{++} flux in neuronal cultures (103). Exposure to alcohol during the late prenatal but not during earlier or neonatal periods reduced NMDA receptor binding in rat hippocampal formation (157).

Dopamine and its metabolite levels were reduced in fetal and young rat brains (51), although these changes may not always persist into adulthood (120). Altered behavioral responses to selective dopaminergic drugs indicated that mesolimbic and nigrostriatal dopamine functions were affected persistently (11,79). Prenatal alcohol exposure altered spontaneous activity of dopamine neurons in the substantia nigra (161), and there were significant differences in responses of nigral or ventral tegmental dopamine neurons to systemic dopamine agonists (161,162). These effects are consonant with morphological indices of delayed dopamine neuron maturation and stunted arborization of pars compacta nigral neurons (163). There were no differences in dopamine-stimulated adenylate cyclase activity or in G-protein concentrations (52). Dopamine dysfunction may underlie locomotor hyperactivity in rodents and perhaps contribute to attentional problems in FAS children.

Changes in other neurotransmitters may certainly contribute to neurobehavioral delays and behavioral dysfunctions in FAS (51). Deficits in radial-arm-maze performance have been associated with increases in the density of hippocampal muscarinic receptors in neonatal mice given 2 weeks of daily injections of alcohol (136), although no significant changes in hippocampal muscarinic receptors were found after prenatal alcohol exposure in rats (195,202). Prenatal exposure to higher levels of alcohol produced 40–60% decreases in serotonin and its metabolites and receptors in neocortex and cerebellum but not in hippocampus (51,106).

NEUROENDOCRINE DYSFUNCTIONS MAY ALTER SENSITIVITY TO STRESS

In addition to CNS neurochemical alterations, prenatal alcohol exposure in rats produced long-lasting changes in hormones (110,192). Biochemical and endocrine responses to stress are increased in rats exposed prenatally to alcohol (192), and this finding may explain behavioral dysfunction in animals in stressful situations (192). Prenatal alcohol altered corticotropin-releasing factor gene expression and increased adrenal sensitivity to adrenocorticotropin (ACTH) (102,145,152) and stress-induced alterations in catecholamines (153). There are also different patterns of sex-influenced sensitivity to ARBDs in animals ranging from behavioral to pharmacological to immunological responses (15,70,79,93,194,204,205). The many outcomes of perinatal alcohol exposure in animals that depend on offspring sex and the altered early endocrine maturation that may mediate these effects have been reviewed by Weinberg (191,192) and by McGivern & Riley (110). For example, prenatal alcohol exposure alters circulating levels of testosterone at perinatal periods when testosterone surges are critical to organizing sex-specific brain structures (109), and the impact of altered sex hormones may persist (101,159). There do appear to be long-lasting effects of prenatal alcohol on sexual maturation in rats (111) and in adolescent girls with FAS (174).

EXPRESSIONS OF BEHAVIORAL/COGNITIVE DEFICITS MAY BE SPECIES SPECIFIC

FAS children show distinctive, persistent and subtle patterns of cognitive dysfunction under increasingly sophisticated psychological assessments (90,175). Cognitive deficits in monkeys, even in the absence of morphological changes, were associated with binge patterns of alcohol exposure restricted to early pregnancy (37), suggesting that a woman who drinks before she knows she is pregnant can endanger the fetus, even without more drinking. Research in rodent models has elaborated the nature of age-dependent behavioral hyperactivity and learning deficits in rodents (117). Spatial and temporal serial pattern learning and memory in rats is disrupted by prenatal alcohol (66,67,98). Hall et al. (72) showed that working memory or spatial learning deficits were present in both younger and older rats, but older rats with prior experience in the maze apparently remembered, showing no deficits in relearning. However, a single in utero episode of high peak BALs in mice was able to produce a profound deficit in memory retrieval in 2-year-old mice that was not evident in 3-month-old mice (55). These results suggest lasting ARNDs (12,150) and/or earlier emergence of memory problems associated with aging. Other reports with neonatal exposure in rats, however, have shown that deficits may appear only in younger offspring (113,114,151). Attentional deficits have not been identified reliably in rats (83), although effects of alcohol exposure on learning tasks may also indicate attention problems (46).

Differential behavioral reactivity or tolerance to alcohol by animals exposed prenatally to alcohol (147) may be due in part to in utero experience with alcohol. Rat fetuses appear to become familiar with and/or develop learned associations with the sensory qualities of alcohol present in the amniotic fluid. This experience can influence fetal and postnatal responses to or preferences for alcohol (28,29,48) and may influence processes associated with the initiation of alcohol intake. Gestational alcohol exposure apparently produces sensitization to maternal alcohol-induced suppression of fetal activity and to intraoral alcohol-induced mouth movements in rat fetuses (30).

GENETIC DISPOSITIONS TO TERATOGENESIS ARE BEING INVESTIGATED

Animal research has facilitated understanding of risk for FAS by systematically manipulating factors directly to assess their role in fetal alcohol effects (4,5). Although social, behavioral and environmental factors can predict risk (5,154), the fact that FAS tends to occur in families and certain groups more than in others has stimulated research to identify gene-based characteristics related to teratogenic sensitivity in animals. For example, long-sleep (LS) mice, bred to withstand longers periods of alcohol's narcotic effects, produced litters with lower birth weight, poorer survival and poorer learning than relatively alcohol-insensitive short-sleep (SS) mice given equivalent amounts of alcohol (64,65). The C57BL/6J mice appear much more sensitive to the teratogenic effects of alcohol than do Swiss Webster (140,144) or SS (64) mice. Young weanling Prefering (P) rats that differ from NonPrefering (NP) rats in preference, tolerance and sensitivity to alcohol showed greater sensitivity to teratogenic effects of early neonatal alcohol exposure on locomotor behavior than did NP rats (151). The difference between P and NP lines was not found in adult rats (113,114). Animal models may provide valuable means to assess gene-based hypotheses of sensitivity to alcohol teratogenesis, for example, by measuring the influence of different forms of alcohol dehydrogenase (ADH) (203). To date, there is little evidence from animal research demonstrating that any particular genotype related to alcohol preference, tolerance or sensitivity may confer specific susceptibility to ARNDs. However, the results of breeding programs selecting for teratogenesis per se have not yet been published, and these types of studies, which are ongoing, are necessary to address this issue.

UNDERNUTRITION IS A KEY RISK FACTOR

Perhaps one of the more important findings from animal research is that nutritional aspects of prenatal alcohol exposure are inseparable from alcohol's teratogenic effects (5,49,61,158). Research in animals has demonstrated that inadequate maternal diets can exacerbate the effects of alcohol and has confirmed that alcohol can directly and indirectly compromise nutritional status (104,105). Protein, carbohydrate, vitamin or mineral deficiency further decreased birth weight (193,201).

CODRUG ABUSE CAN EXACERBATE THE EFFECTS OF ALCOHOL

One of the difficulties in unequivocally attributing birth defects to alcohol in humans is that alcohol abusers frequently abuse other drugs that can also affect fetal development (38,42,86). Combined repeated administration of alcohol and cocaine to pregnant rats further decreased birth weight, delayed physical maturation and increased hyperactivity (33). A single coadministration of cocaine and alcohol to pregnant mice, however, did not alter the teratogenic effects of alcohol alone on fetal morphology (143). Differences in species and/or dosing patterns and in variability or subtley in the teratogenic effects of cocaine in animals (89) may account for the different outcomes in these studies.

Caffeine caused an additive decrease in cultured fetal hepatocyte replication (26) and in birth weight in rats exposed to alcohol in utero (74). The effects of prenatal caffeine were independent of alcohol's effects on gross morphology (59), and the effects of caffeine (but not alcohol) on body weight were diminished by weaning (74). Despite its prevalence and interactive effects with alcohol in humans, there have been relatively few studies of prenatal alcohol combined with tobacco (or nicotine) in animals (but see 13,130).

MECHANISMS OF ALCOHOL TERATOGENESIS

Risk factors are risk factors because they directly or indirectly affect mechanisms of alcohol teratogenesis (5). Several of the most likely mechanisms have been reviewed (5,57,63,119,158). We (5) and others (119,158) have recently argued that hypoxia, free radical damage and perhaps dysregulation of neural trophic factors have the most compelling evidence of the proposed mechanisms (5). The regulation and timing of neural growth processes are controlled by several tissue-specific trophic or growth factors such as retinoic acid, nerve growth factor (NGF), thyroxine and growth-associated protein 43 (GAP43/B50).

The normal physiological substrate for ADH may be retinol (vitamin A) (200,203), which is converted to retinoic acid, a potent morphogen and a regulator of the ADH3 allele. Several researchers have proposed independently that prenatal alcohol acts by competitively inhibiting ADH retinol-metabolism and thereby limiting the conversion of retinol to retinoic acid. This change increases tissue levels of retinol, which can be a potent teratogen, and reduces the bioavailability of retinoic acid (53,68,138). Alcohol has reduced maternal serum levels of retinoic acid in rats (168) and altered levels of cellular binding proteins (169). We reported that alcohol-induced inhibition of neurite outgrowth and GAP43/B50 protein levels in cultured human neuroblastoma cells (LA-N-5) were reversed by retinoic acid (156). The relationship between dietary vitamin A, circulating retinoic acid levels and ADH activity is complex (200) with ADH isoforms, for example, by varying in ability to metabolize retinol. The role of retonic acid in mediating fetal alcohol effects remains to be determined.

Alcohol can also interfere with NGF function. Fetal chick forebrain extracts collected after alcohol exposure had a reduced stimulatory influence on cultured dorsal root ganglia (DRG) neurite outgrowth, without affecting neuronal survival (85). DRG cultures from alcohol-exposed chicks were less sensitive to exogenous NGF (85), and the inhibition of DRG neurite outgrowth by a lower dose of alcohol could be reversed by NGF (84). NGF, but not epidermal growth factor (EGF), reversed a decrease in GABA neuron maturation in chick embryos (22), and the toxic effects of early exposure to alcohol on cholinergic neurons was prevented or reversed by NGF and EGF (20).

NGF limited the loss of cultured neuronlike rat pheochromocytoma tumor cells (PC-12) accompanying high concentrations of alcohol (129). Because NGF arrests proliferation and induces differentiation, these results suggest that proliferating cells may be more susceptible to alcohol. However, differentiation (i.e., neurite outgrowth) of cultured human LA-N-5 cells without added NGF was inhibited by concentrations of alcohol that did not affect cell survival (156). Astrocytes cultured from neocortex of mature rat fetuses exposed to alcohol throughout gestation showed increased concentrations of both cell surface and intracellular NGF receptors and an apparent increase in intracellular content of NGF perhaps caused by decreased NGF secretion (184).

FREE-RADICAL DAMAGE OF MEMBRANE LIPIDS AS A KEY MECHANISM

Anomalies associated with FAS or ARNDs may arise from excess oxygenated free radicals (e.g., O_2-, $OH-$, H_2O_2) that can severely damage neural cells (16,119,128). Membranes and membrane lipids appear particularly susceptible to alcohol-induced free radical damage during development (6,23,45,127). Alcohol increased fluidity of rat brain membranes (186) and microsomes because of metabolic rather than detergent actions (6). Fetal alcohol exposure increased levels of lipid peroxidation in all brain areas measured in rats, including neocortex, hippocampus and cerebellum (134). Alcohol also altered the structure of plasma membranes of proliferating astrocytes in culture (146). Free-radical damage may explain regional sensitivity differences to fetal alcohol exposure because some neurons (e.g., neural crest) have lower levels of antioxidants (e.g., superoxide dismutase) than do other areas (41).

Alcohol exposure also reduced the availability or activity of cellular defenses that normally protect against free radical damage (82). These include decreased glutathione levels in rat brain and reduced levels of α-tocopherol (vitamin E) in rat fetal hepatocytes (45,148,180,190). The availability of antioxidants depends on diet, smoking and other drug use, so that the proposed free-radical mechanism of FAS is consonant with known risk factors for FAS (5,45). Dietary supplementation with membrane-critical lipids such as gangliosides (GM_1) (87,88) or Ω-3 fatty acids (187,189), or with antioxidants such as vitamin E (180) or with micronutrients such as zinc, a cofactor for free-radical scavenging enzymes (180), may mitigate the impact of alcohol on fetuses.

HYPOXIA AS A COMMON FINAL PATHWAY OF ALCOHOL TERATOGENESIS?

The potential key role of hypoxia in alcohol teratogenesis has been reviewed recently (5,119). Prenatal hypoxia can increase the levels of oxygen free radicals (119) and can produce effects very similar to alcohol (91) that can persist into childhood (95). High BALs can collapse umbilical vasculature in monkeys (126) and reduce placental blood flow (60). Suppression of fetal "breathing" movements, a sensitive index of fetal hypoxia, occurs reliably in humans and animals following maternal alcohol (112).

Hypoxia initiates cellular events that have also been documented after prenatal alcohol exposure (cf. 5,119,158). Certain brain areas (e.g., hippocampus) may be more vulnerable to alcohol-induced hypoxia because they are richly vascularized and more densely populated with excitatory amino acid neurotransmitters such as glutamate (47). Hypoxia-related excess release of these neurotransmitters during fetal alcohol exposure may cause excitotoxic cell damage (118).

MATERNAL TREATMENTS

Researchers are evaluating how the impact of alcohol on fetuses might be mitigated by using different treatments on pregnant animals (i.e., prevention) or how the long-term course of neurobehavioral maturation in prenatal alcohol-exposed offspring may be modified by postnatal interventions (treatment). These animal models, however, cannot be used to test treatments of alcoholism during pregnancy because there are no models of alcoholism per se. Tajuddin and Druse (179) reported that the serotonin agonist buspirone, which has been used to treat withdrawal in humans, given to pregnant rats attenuated the effects of prenatal alcohol on serotonin levels in motor cortex but not in somatosensory cortex. Treatment of pregnant mouse dams with aspirin or ibuprofen attenuated the effects of prenatal alcohol on offspring (141,142), whereas pretreatment of neonatal rats with aspirin before neonatal alcohol exposure did not (108). Administration of levamisole to lactating rat dams, however, improved immune function of offspring (172).

Attenuating nutritional deficiencies associated with gestational alcohol in rats may limit alcohol teratogenesis (49). Reducing nutrient deficiencies appears to mitigate some effects of lower doses of alcohol, although fetal alcohol effects do not appear to be eliminated by dietary supplementation beyond nominally adequate diets. For example, vitamin E deficiency leads to greater fetal weight loss due to alcohol, whereas vitamin E supplementation does not prevent growth retardation (180). Hungund et al. (88) reported that maternal dietary administration of gangliosides (GM_1) reduced the impact of alcohol on neurobehavioral outcome in offspring. Similarly, enriching maternal diet with linolenic acid (54) or with Ω-3 fatty acids (187) attenuated fetal alcohol effects. Addition of protein to diets of rat dams (201) or of putrescine to chick embryos attenuated alcohol-induced reductions of fetal and brain weight (160).

TREATMENT OF OFFSPRING

In addition to suggesting underlying neurochemical pathology, shifts in dose responses to psychoactive drugs in animals exposed prenatally to alcohol may indicate potential pharmacotherapies for FAS (cf. 78,80). There are significant prenatal alcohol-induced dose-response shifts in offspring given challenges with dopaminergic drugs, particularly CNS stimulants (120). Differential responses to drugs acting on other neurotransmitter systems (e.g., cholinergic or serotonergic) have not been consistent (80). The value of such research with animals depends on how well specific actions of drugs may match often global cognitive or behavioral outcomes in children (80).

Rearing animals in enriched or complex environments can reliably stimulate CNS development, facilitate recovery of function and enhance behavioral performance. Rearing rats or mice in an enriched environment after prenatal alcohol exposure significantly improved maze learning and ameliorated deficits in motor performance (77,188). However, enrichment did not affect cortical thickness in prenatal alcohol-exposed mice (188) and did not produce normal increases in hippocampal pyramidal cell dendritic spine densities in prenatal alcohol-exposed rats (14). Important features of enriched environments appear to include increased opportunities for diverse movement, complex sensory stimulation and socialization. Any or all of these may be applied to children with FAS to facilitate development and performance.

SUMMARY

Animal models should continue to be productive in increasing our understanding of FAS and ARNDs in children (173). Clearly, the goal of animal research is not simply to show that fetal rodents or chicks can react to alcohol as human fetuses do. The appropriate aims of FAS/ARND research will be to study the nature of common reactions to alcohol, to identify risk factors, to discover mechanisms and to explore potential treatments. Clearly, these goals of understanding, prevention and treatment of FAS/ARNDs cannot be done efficiently or sometimes at all in humans and will demand continued animal research.

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