Environmental Causes of Central Nervous System Maldevelopment

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ABSTRACT. The central nervous system is the most vulnerable of all body systems to developmental injury. This review focuses on developmental processes by which the nervous system is formed and how those processes are known or suspected to be injured by toxic agents. The processes discussed are establishment of neuron numbers; migration of neurons; establishment of connections, neurotransmitter activity, and receptor numbers; deposition of myelin; and 2 processes that are prominent in postnatal development, trimming back of connections and postnatal neurogenesis. Our knowledge of the risks of exposure to environmental hazards in childhood and adolescence is minimal. Most of our information concerns the effects of neurotoxicants in prenatal and early postnatal life. More worrisome than our lack of data regarding later stages of development is the minimal effort that we have mounted to protect the public from known neurotoxic agents and that regulations for testing new drugs and chemicals still do not require any assessment of neuroteratologic effects. Pediatrics 2004;113:1076–1083; CNS development, teratology, critical periods, gene-environment interactions.

ABBREVIATIONS. CNS, central nervous system; MAM, methyla-zoxymethanol; RA, retinoic acid; VPA, valproic acid; GABA, γ-aminobutyric acid.

Of all of the body systems, the central nervous system (CNS) is the one for which we have the most information on normal development and developmental injury, yet it is also the system for which the gaps in our knowledge are greatest. The assembly of the CNS requires many more steps than other systems. A myriad of different cell types must be produced, and some of these must migrate into their final positions. The differentiation of neurons is complex and dependent on neuron activity as well as other influences. The formation of connections between neurons and the setting of transmitter types and receptor levels all are developmental processes that are subject to interference from environmental factors. In addition, the development of the CNS includes periods of cell death and dying back of connections—developmental processes that are rarely seen in other systems and are likely to be influenced by exogenous factors. The addition of myelin to sheath fibers of the central pathways and peripheral nerves is yet another process that is subject to interference from the outside world. All of this is made even more complex by the fact that the sequence of developmental events runs on different schedules for different neuron types. For example, migration of human oculomotor neurons is an early embryonic event, whereas migration of cerebellar granule cells is still ongoing in postnatal life.

The reader should be forewarned that many questions for which pediatricians need answers cannot be answered from the existing literature. Most of the studies in this review are related to prenatal exposure to neurotoxicants. It is well known that prenatal exposures to agents that seem relatively innocuous in adults (eg, ethanol, thalidomide, isotretinoin) can have disastrous effects on the developing brain of the conceptus that would not be predicted from the effects of the same compounds on adults. By extension, it is natural to be concerned that postnatal development of the brain is similarly sensitive to environmental exposures. That injuries and infections in childhood and adolescence can result in many lasting CNS problems, such as mental retardation, hydrocephalus, and epilepsy, increases our concern. However, almost no research has been done to determine whether neurotoxicants have different impacts in children versus adults. Thus, when parents inquire, “Are my children at special risk from the pesticides the exterminator uses?” the answer is, “We don’t know.”

The importance of detecting teratologic injuries to the CNS was not recognized in the initial safety testing guidelines of government agencies, which focused on somatic birth defects rather than functional defects. This is surprising, because the first teratogens recognized, rubella infection1 and radiation,2 both have major effects on CNS function. As more and more CNS teratogens have been identified, guidelines have been adjusted to provide some limited protection.3 Unfortunately, we still find ourselves in the situation in which most of the known CNS teratogens have been discovered in human cases rather than in the laboratory. Even so, teratologic research has given us many ideas about which kinds of agents are likely to be hazardous to the developing CNS and how to test for CNS injury. In the past 10 years, great advances in understanding the genetic control of normal development of the CNS have provided clues to newly identified devel-
opment processes that might be subject to environment interference. This brief review focuses on early discoveries, to emphasize how long we have known that CNS teratogenicity should be a concern, and very recent discoveries, to highlight new research directions in the field.

ESTABLISHMENT OF NEURON NUMBERS

It is obvious that exposure to agents that interfere with cell proliferation can disrupt development. This was first demonstrated in studies of radiation exposure in rodents and later in studies of anticarcinogens. The earliest studies of CNS teratogenesis focused on these exposures and taught us many principles that apply to other classes of teratogens. Whether teratogens prevent cell division or kill proliferating or migrating cells outright, the effect is similar: only those cells that are actively proliferating are reduced in number, and which cells will be affected is determined by the exact stage of development when exposure occurs. Because different neuron populations form at different stages, exposure to the same agent at different times will result in different patterns of morphologic anomalies and different behavioral effects. Morphologic differences with different exposure periods have been reported in many studies using methylazoxymethanol (MAM); this agent provides 1 of the best examples of how exposure time is linked to behavioral outcome. Balduini et al studied spontaneous activity in rats that were exposed to MAM at 6 different exposure times between day 14 and day 19. Groups of animals that were exposed during the mid-fetal period were hyperactive compared with controls. The group that was exposed to the same agent on day 19 was hypoactive. There is nothing inconsistent in these disparate results. Rather, if one examines the brain regions that most actively add neurons during the exposure periods, it is obvious that hyperactivity results when exposures injure the cerebral cortex and hippocampus, whereas hypoactivity follows exposures that injure the cerebellum. Typically, injury of those structures by other means, such as electrolytic lesions, would have the same behavioral effects.

The critical importance of exposure time is only 1 feature of exogenous agents that interfere with neuron production. Another is the way that teratologically reduced neuron numbers are expressed in morphology. Unlike loss of neurons from the mature CNS, which can be seen in reduced density of cells, the typical result of failure of neuron production is a set of neurons with normal density and a reduction in the volume of the structure that they form. Density changes are observed only when the reduction of cell numbers is massive, whereas functional changes can occur with less extreme losses. Yet another feature worth noting is that studies of antimitotic agents do not support the idea that brief insults to proliferation reduce the numbers of all of the cells formed after the exposure has ended. Instead, proliferative tissues seem to rebound from insult and return to producing normal cell numbers. Therefore, whereas populations of neurons that are exposed at the peak of proliferation may show permanent deficits in number, those that are formed subsequently are typically normal in number. The result is that neuron numbers can be reduced in very specific regions, while many parts of the brain seem unaffected.

An important characteristic of the functional impact of early neuron loss is that expression of the deficit may not occur for some time after the injury. For example, MAM exposure during the prenatal proliferation of growth hormone–releasing factor neurons has a dramatic effect on growth but not until after weaning, when growth hormone becomes a critical determinant of growth. Furthermore, aging may increase the expression of both anatomic and behavioral symptoms of developmental injury, as has been shown in animals that were exposed as neonates to triethyltin.

An example of a widespread environmental hazard with antimitotic properties is methylmercury. Data from environmental disasters in Japan and Iraq led to the conclusion that children in utero are much more sensitive to this neurotoxicant than those exposed after birth. Furthermore, their symptoms are different. Studies in animals have revealed that methylmercury exposure arrests mitotic cells in metaphase by disrupting the microtubules of the mitotic spindle. Thus, although the chemical has many mechanisms of neurotoxicity, it has 1 that is particularly injurious to the developing brain. Because most neurons form before birth, prenatal exposure to an antimitotic agent would be especially hazardous to the embryonic or fetal brain.

Environmental exposures need not be antimitotic to lead to failures of neuron production. The discovery that there are families of genes, such as the Hox genes and PAX genes, that are critical to early brain development, along with the discovery that some of these genes respond to teratogens, has opened a new avenue of research in teratology. Retinoic acid (RA) is a potent teratogen because it is the endogenous signal that sets off the HOX cascade. If the level of RA is too high, then genes such as Hoxa1 and HOXB1 produce too much of their protein product. If the level of RA is too low, then the genes produce too little of their products. Both situations lead to birth defects of the CNS. In the future, we are likely to find many more examples of teratogens that act by altering gene expression, and some of the mechanisms will be unexpected. A recent example comes from human and animal studies of the antiseizure medication valproic acid (VPA). It has been known for some time that human offspring who are exposed to this drug have a significantly increased risk of neural tube defects and an even greater risk of neurologic symptoms and developmental delays. Subsequently, case reports began to suggest an association between exposure to valproate and autism. A recent study found that 5 of 46 children who were enrolled in a family support group after in utero exposure met the diagnostic criteria for autism, pervasive developmental disorder, or Asperger syndrome. It has been reported that VPA is even more potent than RA in increasing the expression of Hoxa1 and that this seems to be 1 of the drug’s mechanisms of teratogenicity, but which mechanism could ex-
plain how the drug accomplishes this alteration of gene expression? A recent series of studies demonstrated that VPA is a direct inhibitor of histone deacetylase. Inhibition of this family of proteins causes a change in chromatin structure that increases the availability of some genes for transcription. It may be that VPA’s effect of driving expression of Hox genes is mediated by its inhibition of histone deacetylase.

Soon after their formation, many neuron populations undergo a period of rapid apoptotic cell death that cuts their numbers by half. The process coincides with synaptogenesis of the affected neurons and thus is thought to represent selective retention of those that have been most successful in forming connections. Researchers have identified several trophic factors that influence the programmed death of neurons as well as some of the genes whose expression is required. Thus far, no environmental agents that affect programmed cell death have been discovered.

**MIGRATION OF NEURONS**

A number of teratogenic exposures are known to lead to ectopic neurons, e.g., neurons that should appear in gray matter appear in white matter, instead, as though they failed to reach their normal destination. In most cases, it is not clear whether teratogens interfere directly with the mechanisms involved in the actual process of migration, because many agents that reduce proliferation seem to result in ectopias (e.g., radiation, methylmercury, toluene, ethanol). This suggests that loss of neurons as they are forming eliminates signals that are needed for the migration of those that are formed afterward. For other agents, the mechanism by which migration is disturbed is unclear.

What is more certain is that the timing of migration is well established for many different brain regions. Thus, migration failures sometimes can be used to establish the stage of development when injury occurred. For example, human cerebrocortical ectopias suggest a disturbance of brain development between the fifth or sixth week postconception, when the cortical plate is established, and the fifth month postconception, when virtually all cortical neurons have assumed their final positions.

The genetic control of migration is an area of research in which rapid progress has been made in recent years. As we come to understand more about what attracts moving cells and what repels them, it is likely that environmental factors that interfere with those processes will be identified. For example, it is now known that the function of Reelin, the gene that is abnormal in the reeler mutant mouse, is critical for normal migration in the layered cortical structures of the cerebral cortex, hippocampus, and cerebellum (reviewed by Caviness and Rakic) as well as other structures that undergo migration, such as the facial nucleus. Humans who lack the normal REELIN protein exhibit lissencephaly with cerebellar hypoplasia, whereas increased REELIN expression has been reported in cases of polymicrogyria. Reelin expression is thyroid hormone dependent, suggesting that interference with this protein’s role in migration may be 1 of the mechanisms by which hypothyroidism and hyperthyroidism are teratogenic to the CNS.

Unlike reelin, which is thought to act as a signal to migrating neurons, the gene coding for cyclin dependent kinase 5 (cdk5) is expressed in migrating neurons, themselves. It is thought to play a role in the cytoskeletal processes required for cell movement. The phenotype of the knockout is complex. For example, Purkinje cells fail to reach their normal positions in the cerebellum, whereas granule cell precursors seem to migrate normally to the cortical surface of that structure. Subsequently, granule cell progeny fail to migrate to the internal granule layer. Clearly, the activity of cdk5 is not required for migration by all neurons at all stages of their development, but some neurons require it at some stages.

**ESTABLISHMENT OF CONNECTIONS, NEUROTRANSMITTER ACTIVITY, AND RECEPTOR NUMBERS**

The discovery that handling of neonatal rodents has a lasting effect on the nervous system, modifying the animals’ response to stress as an adult, brought attention to the fact that transient changes in the milieu of developing neurons can have unexpected effects. Release of corticosterone initiates the handling effect, but how this ultimately alters the brain remains unclear, because the event has so many effects on so many parts of the CNS (reviewed by Champagne and Meaney). However, there are surprising new developments. Maternal behavior toward rat offspring shows individual differences, which determine the response to stress in the next generation, and features of an individual mother’s behavior are seen to recur in the mothering behavior of her female offspring. Studies in which pups are raised by their own mothers or reared by unrelated females demonstrate that this transmission of maternal behavior and stress responses is not genetic but depends on the maternal behavior experienced by the pups.

It is now recognized that the processes by which neurons establish their connections, begin to release transmitters, and form receptors for transmitters are targets for many teratogens. Any exposure that alters hormone levels or transmitter levels has the potential to be teratogenic. Furthermore, the chance of human exposure to agents with these properties is great. For example, the widespread use of psychoactive drugs has increased the number of pregnancies in which exposure to transmitter- or receptor-altering drugs occurs. Another example is exposure to pesticides. It should come as no surprise that the most efficient way to control insects is by disrupting the function of either the CNS or the reproductive system. Unfortunately, the transmitter systems and hormone systems of humans are similar to those of insects.

The creation and elimination of synapses is a lifelong process, but the establishment of the basic pathways is essential to later development. Several environmental factors have been shown to reduce the number of connections formed by neurons during
development. For example, protein malnutrition,\textsuperscript{48} hypothyroidism,\textsuperscript{49} and lead exposure\textsuperscript{50} of the postnatal rodent seem to disturb this process in cerebral cortex.

Studies of the ontogeny of transmitters and their receptors have yielded many surprising results. First, the distribution of these elements in developing brain differs from the distribution seen in adults.\textsuperscript{51–54} This fact has led to the recognition that the signaling functions served by transmitter systems may differ at different stages of development. For example, the transmitters \(\gamma\)-aminobutyric acid (GABA) and glutamate seem to act as chemotactants to migrating cortical neurons in the rat and the mouse, respectively.\textsuperscript{55,56} and glutamate serves the same role in the cerebellum.\textsuperscript{57} The presence of GABAergic fibers is thought to promote differentiation of monoaminergic and peptidergic neurons.\textsuperscript{51} Although GABA is the major inhibitory transmitter in the mature CNS, it has been shown to be excitatory to neurons in the developing hypothalamus.\textsuperscript{58} Because the firing of neurons plays a role as they differentiate to assume their final transmitter characteristics,\textsuperscript{59} understanding what depolarizes developing neurons is an important field of investigation.

These examples make it clear that environmental exposures that inhibit or mimic transmitter activity are likely to disrupt development of the CNS. The possibility has been confirmed for several psychoactive drugs. A classic case is that of prenatal exposure to haloperidol. Brief prenatal exposure of rats provokes a decrease of dopamine receptor numbers that persists after birth. The critical period for the lasting effect is when dopamine receptor numbers are being established.\textsuperscript{60} At the same time, muscarinic cholinergic receptor activity is increased,\textsuperscript{61} suggesting that exposure permanently alters the type as well as the number of receptors expressed by neurons when they receive abnormal input at certain stages of development. Diazepam is another example of a drug that affects receptors transiently in the adult but has lasting effects when the fetal brain is exposed. Adult norepinephrine levels in the hypothalamus are significantly reduced, and the stress response, as reflected in plasma corticosterone levels, is suppressed in exposed animals when they reach maturity.\textsuperscript{62,63} As with haloperidol, there is a critical period for diazepam’s teratologic effects. It occurs at the time when benzodiazepine receptors are appearing, and blocking those receptors while diazepam is present eliminates the teratologic outcome.\textsuperscript{62}

Nicotinic receptors are of special concern because of the possibility of exposure from maternal smoking and second-hand smoke. Nicotine exposure during neurulation has been shown to interfere with neuron survival in cultured rat embryos.\textsuperscript{64} Behavioral studies suggest that males exposed in utero respond to a postnatal nicotine challenge with exaggerated locomotor activity, whereas females do not.\textsuperscript{65}

There is no question that adolescence is a period when the brain is undergoing maturational changes, so there is good reason to suspect that environmental factors might have important developmental consequences during this period (reviewed by Adams et al\textsuperscript{66}). Nicotine is 1 of the few teratogenic agents that have been studied for teratologic effects in the adolescent rodent. For obvious reasons, researchers are concerned that nicotine exposure of adolescents may be more addictive than later exposures. In a recent series of studies,\textsuperscript{67,68} adolescent rats that were exposed to nicotine showed less obvious effects on measures of neuron number and neuron size than rats that were exposed in utero. However, they did show long-lasting changes in noradrenergic and dopaminergic function, including aberrant responses to a nicotine challenge.

Neurotoxicologists use the term “endocrine disrupters” to describe agents that are hormones, mimic the effects of hormones, or alter hormone status. Thyroid hormones and corticosterone have been mentioned in earlier sections of this review. Sex hormones have long been known to have organizing effects on the developing nervous system that lead to permanent changes in many sexually dimorphic behaviors, from rough and tumble play to reproductive behaviors to tolerance for salt and saccharine in drinking water. The critical period for such changes in the rodent extends from fetal to neonatal life, whereas in primates, including humans, the critical period occurs before birth.

A number of teratogens have been found to alter sexually dimorphic behaviors. Of these, the ones most studied in humans are synthetic progestins. Offspring who were exposed prenatally attained significantly higher scores on a paper-and-pencil test of potential for aggressive behavior than their unexposed same-sex siblings.\textsuperscript{69} In addition, tests of offspring indicated lasting effects on such personality variables as independence and self-assurance.\textsuperscript{70} In animal models, also, synthetic progestin exposure during development affects later behavior. For example, Whalen et al\textsuperscript{71} found marked changes in sexual receptivity of adult female rats that were exposed to progestins in prenatal life.

Examples of teratogens that are not hormones but alter sexual differentiation of the brain include cocaine, ethanol, and nicotine. The volume of the sexually dimorphic nucleus of the preoptic area\textsuperscript{72} in male rats is significantly reduced by perinatal exposure to cocaine.\textsuperscript{73} Neonatal exposure to ethanol feminizes the preference of male rats for saccharine-sweetened water.\textsuperscript{74} Prenatal exposure to ethanol alters both saccharine preference and maze learning in rats, making females behave more like males and males behave more like females on these sexually dimorphic measures.\textsuperscript{75} Studies of prenatal nicotine exposure demonstrate that it can abolish the testosterone surge characteristic of male rats on the 18th day of gestation and that exposed males exhibit a feminized saccharine preference as adults.\textsuperscript{76}

**DEPOSITION OF MYELIN**

Like other developmental events in the CNS, deposition of myelin runs on different schedules in different regions. A team of investigators has provided a schedule of postnatal human myelination that
highlights the status of many regions in the period when myelination is proceeding most rapidly, from birth to 24 months. Their survey of 62 sites in 162 autopsied infants describes both the median age when myelin is mature and the variability with which milestones of maturity are reached. As examples of white matter that myelinates early (50% of cases by 68 weeks or less), the authors cited the optic tract, the corticospinal tracts of the midbrain and pons, and the middle cerebellar peduncle among regions that show >10% myelination at birth. Among regions that lack myelin at birth, early maturity was observed in the optic and auditory radiations and the body and splenium of the corpus callosum. In the period between 70 and 107 weeks, the pyramids, the lateral cerebellar hemispheres, and the radiations to the frontal, parietal, and occipital cortices reached maturity in 50% of cases. Later-maturing regions include the corticospinal tracts at the cervical, thoracic, and lumbar levels; the globus pallidus; the frontal and temporal poles; and the mamillothalamic tract. Regions that mature past the period surveyed (after 144 weeks) include the tractus solitarius, the corticospinal tract, the corticospinal tracts of the midbrain and pons, and the middle cerebellar peduncle among some parts of the CNS, particularly the dentate gyrus of the hippocampus. The same replacement of old neurons with new is likely to occur in humans.

POSTNATAL BRAIN DEVELOPMENT

Development of the CNS does not end at birth but continues through infancy, childhood, and adolescence. Because development processes are vulnerable to disruption by agents that may not be toxic to mature systems, it is reasonable to expect that the later stages of brain development present special risks. That expectation is confirmed by the known effects of exposure to agents such as lead, which causes lasting brain damage in children at doses well below those that produce toxicity in adults. Both prenatal and postnatal lead levels are inversely correlated with IQ.

This pattern is far from universal. For example, prenatal methylmercury exposure interferes with brain development at much lower doses than postnatal exposure, and behavioral effects of polychlorinated biphenyls are related to prenatal exposure levels, although the doses delivered in breast milk are higher than those received in utero. Completion of the blood-brain barrier at approximately 6 months protects infants and children from some exposures, but it does not account for differential sensitivity in all cases. For example, methylmercury is transported across the barrier freely at any age. A more likely reason for the apparent sensitivity of the prenatal CNS is that many vulnerable developmental processes are completed before birth. In addition, the rapidity of events in the embryo and fetus makes them subject to even very brief exposure to hazards, whereas the slower progress of later development is likely to be more affected by chronic exposures. Developmental events around the time of puberty could be an exception, and they are beginning to receive some attention.

Two processes that might be vulnerable to environmental interference in childhood and beyond have not been studied by teratologists. The first is pruning back of connections, often called "pruning." The number of synapses in the human brain is thought to peak at approximately age 2 and decrease by 40% to the adult number during adolescence. Unfortunately, because we have not identified any environmental factors that reduce or increase pruning, it is not clear how to study what happens to brain function when the process is altered. Increasing information on the molecular mechanisms by which pruning occurs may identify manipulations that can be used to answer this question. In the meantime, at least 1 developmental disorder—autism—has been found to have a substantial number of individuals with above-average head size, which seems to reflect a large brain. Some of the subjects had increased head size at birth, but in most, the growth trajectory seemed to shift in childhood. No one knows whether increased brain size plays a role in the symptoms of autism, but results such as these make investigators wonder whether this could be an example of a deficit in pruning.

Neurobiologists long believed that neurogenesis in the human ended during the first months of postnatal life, but recent rodent and primate studies demonstrate that there is lifelong neuron production in some parts of the CNS, particularly the dentate gyrus of the hippocampus. The same replacement of old neurons with new is likely to occur in humans. What is the role of this process in the normal CNS, and what would happen to function if the process were disturbed? Because many agents that disrupt neuron proliferation are known, scientists are likely to answer these questions soon.

CONCLUSION

A number of excellent reviews cover parts of the material discussed in this article and extend to other areas. Adams et al and Rice and Barone reported the findings of a workshop organized to identify critical periods of teratologic vulnerability in children. Herschkowitz et al described neurobiologic development as it relates to behavior in the first year of life. A chapter by Jensen and Catalano focuses on brain morphogenesis and developmental injury. For readers who want to learn more about the times when different neurons form, there is a comprehensive summary of neuron birthdating studies in rats, with extrapolation to human neurogenesis. A special issue of Neurotoxicology and Teratology was devoted to the question of whether teratologic results of animal studies parallel the results in humans. It reports the proceedings of a conference held to compare human and animal data on the developmental neurotoxicity of various teratogens. The evidence supports comparability across species for both the...
outcome measures affected and the doses at which effects occur.

Pediatricians know that they receive little or no training in embryology or teratology of the CNS in medical school or residency programs, but they may be surprised to learn that the same lack of training exists in all specialties, including obstetrics and gynecology. To the credit of the American Academy of Pediatrics, it now offers an online continuing medical education course in early brain and child development.

The pediatricians who reviewed this article suggested that it should include a reminder to the reader that pediatricians have many opportunities to make a difference in the prenatal development of children. In fact, no specialty has more contact with women of childbearing age in the preconceptional period, which is known to be of paramount importance for prevention of some birth defects, such as neural tube defects. Mothers of pediatric patients and adolescent girls are important target audiences for preconceptional counseling. The March of Dimes has developed a program of slides and notes to train clinicians in assisting their patients and screening checklists for evaluation of preconceptional health (www.modimes.org—search site for “preconception”). There is a special module for pediatricians.

Most reviews end with a call for more research, and no one can doubt that there are enormous gaps in our knowledge of the causes of CNS maldevelopment. However, what is most discouraging in this field is not the limitations of the information available but the limited use that we have made of that information in protecting children from environmental factors that cause CNS injury. If a pediatrician were to read only 1 article from this reference list, then it should be the article by Kimmel and Makris. It reviews the present status of regulations and guidelines. Using the screening methods now in place, virtually none of the human teratogens mentioned in this review would be detected as hazardous to the developing brain of test animals at doses already known to cause lasting impairments of the human CNS.

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