Environmental Health Perspectives
Vol. 74, pp. 177-184, 1987

Steroid Hormones and Brain Development: Some Guidelines for Understanding Actions of Pseudohormones and Other Toxic Agents

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Gonadal, adrenal, and thyroid hormones affect the brain directly, and the sensitivity to hormones begins in embryonic life with the appearance of hormone receptor sites in discrete populations of neurons. Because the secretion of hormones is also under control by its neural and pituitary targets, the brain-endocrine axis during development is in a delicately balanced state that can be upset in various ways, and any agent that disrupts normal hormone secretion can upset normal brain development. Moreover, exogenous substances that mimic the actions of natural hormones can also play havoc with CNS development and differentiation.

This paper addresses these issues in the following order: First, actions of glucocorticoids on the developing nervous system related to cell division dendritic growth and neurotransmitter phenotype will be presented followed by a discussion of the developmental effects of synthetic steroids. Second, actions of estrogens related to brain sexual differentiation will be described, followed by a discussion of the actions of the nonsteroidal estrogen, diethylstilbestrol, as an example of exogenous estrogenic substances. The most important aspect of the potency of exogenous estrogens appears to be the degree to which they either bypass protective mechanisms or are subject to transformations to more active metabolites. Third, agents that influence hormone levels or otherwise modify the neuroendocrine system, such as nicotine, barbiturates, alcohol, opiates, and tetrahydrocannabinol, will be noted briefly to demonstrate the diversity of toxic agents that can influence neural development and affect personality, cognitive ability, and other aspects of behavior.

Because of the growth of neuroscience as a discipline and the increasing recognition of pervasive influences of hormones on brain development and adult brain function, many opportunities exist for expanding our knowledge regarding the actions of environmental toxicants.

Introduction

The brain is a target organ for the actions of hormones secreted by the gonads, adrenals, and thyroid gland, and this sensitivity to hormones begins in embryonic life with the appearance of hormone receptor sites in discrete populations of neurons. Because the secretion of hormones is also under control by its neural and pituitary targets, the brain-endocrine axis during development is in a delicately balanced state that can be upset in various ways. Thus, any agent that disrupts normal hormone secretion can upset normal brain development. Likewise, exogenous substances that mimic the actions of natural hormones can also play havoc with CNS development and differentiation. This article will examine both types of effects, but we shall place special emphasis on the actions of synthetic or natural substances that mimic actions of natural hormones. However, let us first consider the hormone receptors.

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Hormone Receptors in Brain

The brain responds to all six classes of steroid hormones (androgens, estrogens, progestins, glucocorticoids, mineralocorticoids, and vitamin D) and contains receptors for them, as well as for thyroid hormone (*1*). All of these hormone receptors are proteins that contain a hormone-recognizing domain and a domain that binds to specific DNA sequences (*2*). Thus, these receptors exert their effects by binding to specific enhancerlike elements of the genome and modulating (increasing or decreasing) gene expression. Because most of these receptors begin to be expressed in neurons during embryonic life, their presence allows hormones or other molecules that mimic hormone actions (pseudohormones) to affect brain development. Generally speaking, such effects involve induced growth or inhibition of growth of selected groups of neurons, as well as promotion of differentiation of neurotransmitter phenotype or regulatory phenotype (*3*).

The brain does not remain responsive in the same

way after the period of early development is finished. Instead, when neuronal number is stabilized and synapses are laid, the same hormonal signals are able to cause other effects. These effects include reversible modulation of morphology and neurochemistry, which accompany the reversible modulation by these hormones of neuroendocrine function and behavior. However, when brain damage occurs, developmental programs are reactivated to a limited degree, and hormones once again acquire the ability to influence neuronal growth and synapse formation. What determines which hormone effects will occur at a particular developmental stage? It is unlikely that the hormone receptors change; rather, changes at the genomic level are more probable, alterations that determine which genes are turned on or off by the hormone-receptor complex. Let us now examine specific hormone systems.

Glucocorticoids, Neural Receptors and Developmental Abnormalities

Glucocorticoid Receptors in Neural Tissue

Glucocorticoid receptors are present in fetal brain tissue (*4*) and are implicated in a variety of perinatal effects of exogenous and endogenous hormone. Figure 1 shows Scatchard analysis profiles of embryonic rat forebrain tissue at various ages, demonstrating an apparent decrease in binding capacity from fetal day 16 to birth, after which a postnatal increase in binding takes place (*4*). Glucocorticoid administration to rats at birth delays eye opening (*5*), inhibits dendritic development (*6*) and myelination (*7*), and delays appearance of pituitary-adrenal rhythmicity (*8–10*). Reduced brain size and cell number are also reported to result from perinatal glucocorticoid administration (*11*), and this may be a consequence of glucocorticoid-inhibition of cell division (*12–13*).

Glucocorticoids also promote development of the adrenergic phenotype in neurons of the autonomic nervous system (*14*), and they are required for normal maturation of the brain serotonin system (*15*). In the rat, the first postnatal 2 weeks is a stress nonresponsive period that is characterized by reduced corticosterone secretion in response to stress. It is during this time that glucocorticoid administration produces the deleterious effects noted above. Also during this time, handling of newborn rat pups will cause developmental changes that result in greater exploratory activity and less fear in adult life, accompanied by an increased glucocorticoid receptor capacity in the hippocampus (*16,17*). This increased capacity to respond to glucocorticoids, which appears to be developmentally mediated by increased thyroid hormone output, results in a greater capacity of the adult animal to shut off stress-induced glucocorticoid secretion (*16–18*). Thus, neonatally handled rats are better adapted to cope with stress, and there is initial evidence that such animals may age more slowly (Meaney, personal communication). Let us now examine some glucocorticoidlike actions of pseudohormones.

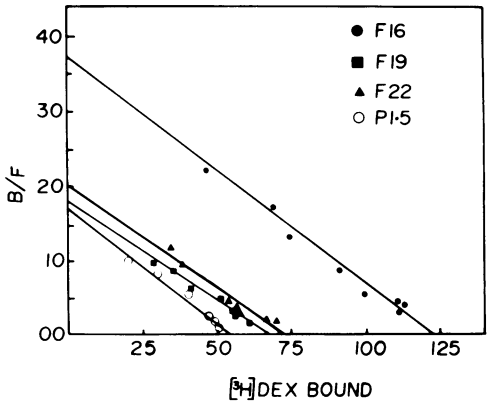

FIGURE 1. Representative Scatchard plots based on saturation experiments with fetal (F16, F19, F22) and postnatal (P1.5) pups using [^{3}H]DEX. Binding capacities (fmole/mg protein) and dissociation constants (Kd in nM) are as follows: F16–111, 4.8; F19–65, 3.6; F22–72, 5.6; P1.5–61, 3.5. Reproduced by permission (*4*).

Synthetic Progestins—Androgenic and Glucocorticoid Effects

Synthetic progestational steroids were administered to pregnant women to prevent miscarriages or were given in the course of pregnancy testing, or were ingested as oral contraceptives after fertilization had occurred. The unanticipated and deleterious side-effects of their administration appear to be due to the ability of these steroids to act as pseudohormones. Specifically, they appear to act as androgens and there are indications that they act as glucocorticoids. Virilizing, androgenlike effects of synthetic progestins were noted on genital appearance (*19*), and the effects were subsequently extended to include psychosexual identity (*20*), other aspects of personality (*21*), and potential for aggression (*22*). Less well known and not as thoroughly studied are influences of synthetic progestins leading to mental retardation, craniofacial abnormalities, and growth retardation (*23*). Although the mechanism of action for these effects is not known, one possibility is that some of the synthetic progestins mimic glucocorticoids and may be acting as pseudoglucocorticoids to produce these abnormalities. One of the most prominent of these steroids, Provera, is a synthetic progestational steroid, which is also a potent glucocorticoid (*24,25*). Glucocorticoids are known to cause cranial malformations (e.g., cleft palate) (*25,26*) and to retard neural growth and development. Additional studies are called for in order to explore this aspect of synthetic progestin action, especially in view of the extensive use of synthetic progestins in obstetric and gynecological practice.

Dexamethasone. Another potential toxin is the synthetic glucocorticoid dexamethasone (DEX) (*27*). When given to rhesus monkey fetuses *in utero*, it causes large-scale destruction of neurons in the hippocampal formation (*28*). What is not clear is the extent to which systemically administered DEX, given to the mother,

will cause similar defects in the fetus. Studies on human pregnancy indicate that DEX given to the mother does not effectively suppress pituitary-adrenal activity in the fetus (*29*). Therefore, it may not effectively cross the placenta in the human, even though maternally administered DEX has been reported to have some effect on the fetus, i.e., to reduce respiratory distress syndrome in subsequent premature offspring (*30*). What appears to be at issue is the existence of an effective mechanism whereby fetal levels of DEX are kept under control. The rat is another species in which maternally administered glucocorticoids are less teratogenic than in other species (*27*). The rat shows limited fetal responses to maternally administered DEX (*31*), including cleft-palate syndrome (*27*), although DEX is apparently actively transferred from the fetus to the mother and kept at a low level (*32*). Thus, it would appear that teratogenic effects of DEX are possible in human as well as in rat fetuses, although there appears to be an efficient protection mechanism in the fetal-placental unit which reduces the potency of maternally administered steroids. It remains to be established how effective similar mechanisms are with respect to synthetic progestins such as Provera.

Actions of Estrogens and Pseudoestrogens on Brain Development and Psychosexual Differentiation

Estrogens are potent agents with respect to brain development. A key element in understanding their potentially teratogenic effects is appreciating not only how they affect normal brain development but also how the fetus is protected from estrogen action. Estrogen receptors (ER) develop during fetal life in brains of both males and females, as shown in experiments carried out on the mouse (Fig. 2) and rat (Fig. 3). Once they have appeared, neural ER are occupied in males, but apparently not in females, by estradiol derived from the local conversion of testosterone to estradiol via aromatizing enzymes (*33,34*). The testosterone is secreted during a perinatal period of testicular activity. Aromatizing enzymes are present in high levels in fetal hypothalamus and limbic brain (*35*). Differential occupancy of ER in males leads to differential effects on neural development and differentiation. These actions include effects on growth of neurites (*36*) that lead to morphological (*37*) and biochemical (*34*) sex differences. In this way, some of the masculinizing and defeminizing actions of testosterone on brain development are produced. Other actions of testosterone on sexual differentiation of the brain are mediated by androgen receptors that, like estrogen receptors, are also expressed equally in male and female brains but are differentially occupied in males because of the testicular secretion of testosterone during perinatal development (*33,34,38*). Paradoxically, these actions of testosterone can be inhibited by estrogens because of their ability to inhibit the secretion of gonadotropins which stimulate testosterone secretion by the testes (*39*).

Cerebral Cortex

One developmental effect of estrogens has potentially great implications for cognitive performance. Estrogen receptors are expressed transiently in the developing cerebral cortex in male and female rodents (Fig. 4) (*33,40*). Progestin receptors are also produced in overabundance during the perinatal period (Fig. 4). Strangely, estrogen receptor content is higher in the right cortex of the female and in the left cortex of the male on postnatal days 2 to 3; structurally, ovariectomy reverses the normally greater thickness of the left cortex as compared to the right, leading to the supposition that estradiol normally inhibits growth of the cortex (*41*). It should be noted that growth inhibition in cortex by estradiol is an effect that is opposite to that noted for estradiol in the hypothalamus and preoptic area (*36*). This is a paradox that must be resolved by further research. In males, castration reduces brain weight and partially reverses the greater thickness of the right cortex as compared to the left (*41*), indicating that testosterone secretion also has a developmental influence on the cortex. One possibility is that testosterone exerts this effect via aromatization to estradiol, and some evidence that cortex has aromatizing capability has recently been produced by MacLusky and colleagues in New Haven (*42*). In the developing rhesus monkey brain, ER, as well as androgen receptors, are found in cerebral cortex, as well as in hypothalamus and limbic brain (*42,43*).

Psychosexual Differentiation and DES

Further insight into actions of estrogens on brain development has come from studies of offspring of mothers exposed to the pseudoestrogen diethylstilbestrol (DES) during pregnancy (*44–46*). In studies thus far completed and published, prenatal DES alters general measures of personality and leads to altered patterns of sexual behavior in adolescence and adulthood that reduce formation of heterosexual relationships (*44*). These differences from carefully matched normal subjects could not be explained by sexual dysfunctions such as vaginismus and dyspareunia, which were low in both groups, but rather appear to be due to psychosocial and neuroendocrine factors related to DES exposure (*44*).

DES is also reported to have a paradoxical masculinizing effect in some human infants exposed to this agent alone during gestation (*47*). A similar observation was made by Greene et al. (*39*) on rats. The explanation for this action is obscure: DES is not an androgen, although some DES-exposed women show elevated testosterone levels as adults and thus may be responding to DES with abnormal androgen production (*44*).

Protective Mechanisms

Since the developing brains of both sexes are highly sensitive to gonadal hormones, what mechanisms guar-

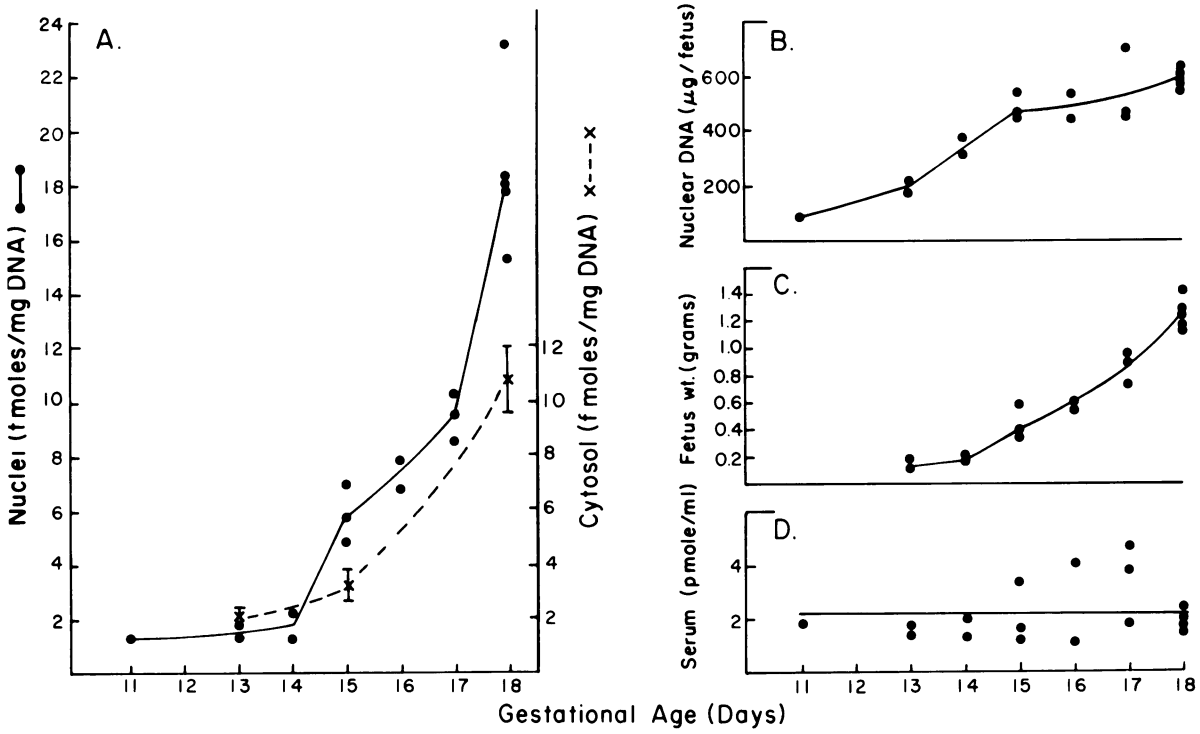

FIGURE 2. Growth in the population of estrogen receptors in the brains of mice during the gestational days 11–18, revealed (*A*) through increased binding of the synthetic estrogen [^{3}H]moxestrol and/or metabolites (fmole/mg DNA) to estrogen receptors in cytosol (●) and to receptors translocated from cytosol to nuclei of cells from whole brains (—). Moxestrol was used because, unlike estradiol, it does not bind to fetoprotein, a protein in the serum produced by the liver of perinatal mice. The population of receptors in nuclei and cytosol began to increase markedly around fetal day 15. Binding to estrogen receptors, corrected for nuclear DNA (*A*), increased with age; total radioactivity in serum remained level (*D*), as both cell nuclear DNA content (*B*) and fetal body weight (*C*) rose. Reproduced by permission (*40*).

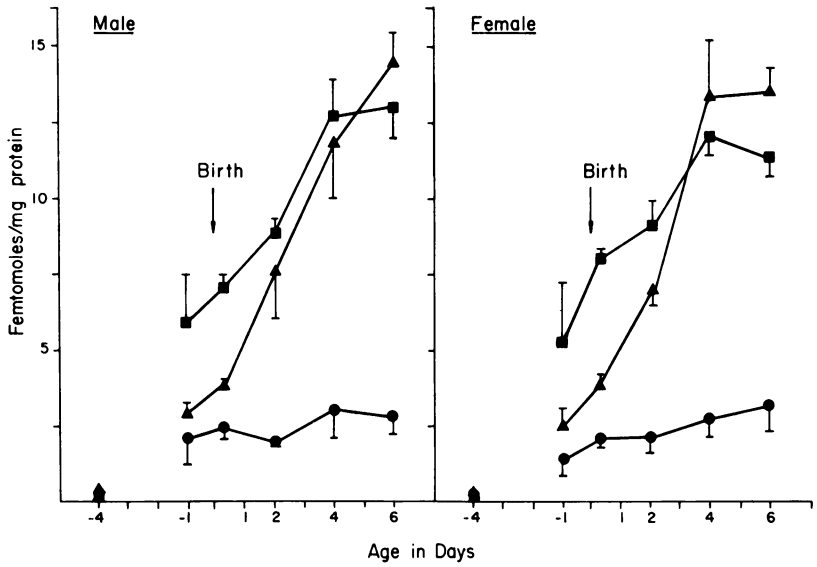

FIGURE 3. Perinatal ontogeny of soluble cytoplasmic estrogen receptor sites in the brains of male and female rats. Cytosols were prepared from either midbrain and brain stem (●), cerebral cortex (▲), or pooled hypothalamus, preoptic area, and amygdala (■) and were labeled *in vitro* with 2 nM [^{3}H]moxestrol. Receptor-bound radioactivity was measured by Sephadex LH-20 gel filtration. Each data point represents mean (±SEM) of four determinations at each age. Reproduced by permission (*53*).

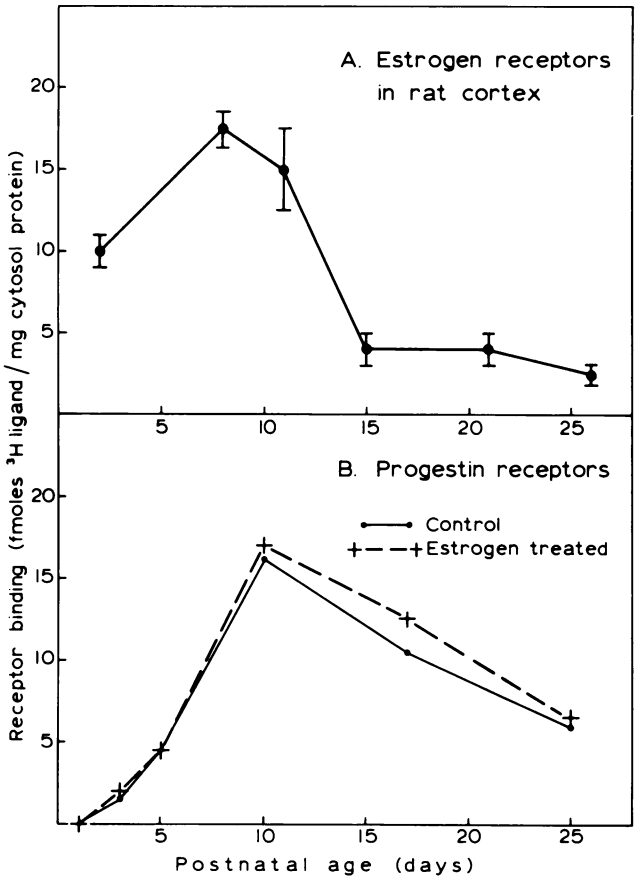

FIGURE 4. Summary of ontogenesis of estrogen and progestin receptors in rat cerebral cortex as a function of postnatal age in days. Reproduced by permission (*33*).

antee that fetuses will not be affected by circulating estrogens and androgens in the mother? One mechanism which has received considerable attention in rodents is the serum binding protein α-fetoprotein (AFP), which binds estradiol in rats and mice (*48*). Because AFP does not bind synthetic estrogens such as DES, DES is much more potent in altering brain sexual differentiation than estradiol (*48*). Where is the protective action of AFP most important, during fetal life or in the postnatal period? Because the critical or sensitive period for effects of testosterone on sexual differentiation mediated by estradiol is postnatal in the rat and mouse, it seems most likely that AFP is most important postnatally when estradiol in the mother's milk might otherwise lead to defeminization and sterility in the female. Why do other species such as the guinea pig and human lack an AFP with estradiol binding capability? A possible explanation is that the defeminizing actions of testosterone mediated by estradiol take place *in utero* in these species; hence, the estrogen binding domain of AFP may have been lost during the course of evolution of these species because it serves no useful protective role postnatally.

Whether or not this explanation is valid, the fetal-placental unit must be examined very carefully for the protection it affords, because it must be important in the human in the absence of estrogen binding AFP. As is the case for dexamethasone, the placenta-fetal unit acts to control the level of estradiol. It does so by selectively secreting estradiol toward the maternal circulation (*49*). In addition, the conversion of estradiol to the less potent estrone is an important factor, and the fetus has substantially higher levels of estrone relative to estradiol than the mother (*49,50*). In contrast to estradiol, the synthetic estrogen DES is passed to the fetus in unchanged form, where it can act potently as an estrogen; the oxidoreductase that converts estradiol to estrone is ineffective on DES, and fetal conjugation of DES to a sulfate ester is not an especially effective removal mechanism (*50*). Thus, the fetal-placental inability to deal effectively with synthetic estrogens such as DES is analogous to the inability of AFP to bind DES; in both cases, DES has preferential access to fetal estrogen receptor sites because it bypasses the mechanism that operates to retard estradiol. What are the implications of this state of affairs for the estrogens in the environment?

Environmental Pseudoestrogens

Many substances in the environment have estrogenic properties, including certain natural products of plants, a number of insecticides, and the stilbene derivatives, of which DES is an example (Table 1). A common feature of all of these estrogens is a phenolic ring that fits into the proteinaceous estrogen receptor. Although the absolute potency of these estrogens depends on the rest of the molecule, especially on the presence of another hydroxyl group some distance away, the primary phenolic hydroxyl group in a great variety of molecules is able to promote estrogen receptor activation (*51*). What can be said about protection of the fetus from such substances? For DES, the lack of an oxidizable hydroxyl group is apparently one of the factors that renders it insensitive to the fetal-placental barrier described above. Other natural and synthetic estrogenic substances in Table 1 appear to share this property. Therefore, to the extent that they may reach the fetus in sufficient amounts to react with estrogen receptors, the ability of the placental-fetal unit to reduce their potency

Table 1. Examples of substances in the environment that have estrogenic activity.

Class of substance	Specific example
Plant estrogens	Isoflavones (daidzein)
	Coumestans (coumestrol)
	Resorcylic acid lactones (zearalenone)
Insecticides	Kepone
	Methoxychlor
	DDT
Synthetic pseudoestrogens	Diethylstilbestrol
	Indenestrol

Based on McLachlan (*51*).

is questionable. However, we must admit our lack of definitive information, because there are no studies to date of most of these substances with respect to penetration from the mother into the fetus.

Indirect Influences of Other Environmental Toxic Agents on Neuroendocrine Function

This brief survey would be incomplete without acknowledging the potentially important effects of other substances in the environment that can alter endocrine function, though they do not act as pseudohormones. What these substances do is act on neurons that are involved in controlling hormone output via the hypothalamic-pituitary axis. Through this axis, output of gonadal and adrenal steroids and thyroid hormone can be altered. In addition, at least some of the pituitary hormones like MSH can have long-term developmental effects on the brain (*52*).

Among the substances that are able to influence gonadal function during development are nicotine, neuroleptics, barbiturates, amphetamines, tetrahydrocannabinol (THC), opiates, and alcohol (*52*). In particular, nicotine, phenobarbital, THC, morphine, and alcohol all are reported to reduce serum levels of testosterone in developing male fetuses and therefore can reduce the masculinization and defeminization of those affected individuals (*52*).

Conclusions

This brief survey summarizes some of the growing body of evidence that the developing brain is an important target organ for the action of steroid hormones. Neural sensitivity to adrenal and gonadal hormones begins during embryonic life, and during the period of early development the nervous system responds to hormones by altering cell proliferation, neuronal growth, and differentiation. These effects are produced via receptor sites that are expressed in neural cells during early development that activate the genome to increase or decrease expression of specific gene products.

The normal effects of steroid hormones on brain growth and differentiation are just now coming under intensive investigation, and the full range of their impact remains to be fully appreciated. For example, we are just beginning to be aware of the effects of gonadal steroids on cerebral cortical development. These effects may be particularly important during the early postnatal period in the human infant when lateralization of hemispheric function is being established and language ability, as well as spatial ability, is being determined. In addition, it is increasingly apparent that gonadal steroid may play an influential role in neural development in the female (*36,41*), even though the traditional dogma is that gonadal steroid effects are exerted more or less exclusively during development in the male to produce brain sexual differentiation.

From the standpoint of environmental toxins, one important lesson of this new information about hormones and brain development is that one must not take for granted the protection afforded the fetus by the fetal environment or the inaccessibility of the developing brain from the rest of the fetal and maternal environment. As exemplified in studies of exposure to DES *in utero*, important behavioral effects of exogenous pseudohormones do occur, and they are amenable to investigation by rigorous psychological testing procedures. The psychological data for DES exposure must now be supplemented by neurological testing by means of noninvasive techniques in order to provide a more concrete organic basis for understanding what DES has done to the brain during development. At the same time, it is imperative that studies be undertaken to determine the ability of other pseudohormones found in the environment to bypass placental protection mechanisms, as is the case for DES, and to gain access to the fetus in amounts that may cause abnormal neural development. It is not clear which of the substances listed in Table 1 may be metabolized by the mother, placenta, or fetus in such a way as to render them less dangerous and which agents in Table 1 lie outside of this protective capability.

Finally, confining attention just to pseudohormones would be a mistake. Many commonly used substances, including alcohol, marijuana, tobacco, and barbiturates alter hormone secretion in fetuses and neonates as well as in adults (*52*). We now appreciate that any disturbance in hormone secretion can contribute to an alteration in neural development. At the very least, such disturbances in development will contribute to individual variability in personality and behavior; at the worst, such developmental alterations may increase the susceptibility to nervous and mental diseases later in life. It is conceivable that changing patterns of drug use and other exposure to behavioral teratogens in the environment may alter frequencies of diseases such as depressive illness and anorexia nervosa. This theoretical possibility should be given some consideration in examining the frequency and sex distribution of such nervous and mental disorders.

Research in the author's laboratory is supported by NIH Grant NS07080 and by NIMH Grant MH41256. Institutional support from the Rockefeller Foundation for research in reproductive biology is also acknowledged. Inna Perlin provided editorial assistance.

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