Mechanisms Underlying the Behavioral Teratogenetic Effects of Chemicals on the Developing Brain

D. Swaab and M. Mirmiran

Although various clinically used drugs are known to threaten fetal brain development, there is no indication of a reduction in the number of prenatally prescribed medicines. A retrospective survey in Belgium showed that an average of 4.4 different drugs had been taken by expectant mothers (Meire et al., 1979), whereas this type of survey only traced 30% of the medicines actually used (Bodendorfer et al., 1979). A prospective survey disclosed that, in the United States, women take on the average eleven different drugs in the course of pregnancy (Doering and Stewart, 1978). In The Netherlands and the Federal Republic of Germany some 80% of the pregnant women take medicines as if pregnancy is a rather serious, longterm disease! Many of these preparations in fact contain a mixture of pharmaceutical compounds, and most of them are of the type that easily cross the placenta. Subsequently they readily reach the foetal brain, since the blood-brain barrier at this stage of development is not capable of preventing their passage. Probably because of the thalidomide tragedy, our awareness of the dangers of drug ingestion has cautioned us against the indiscriminate use of medicines only during the initial stage of pregnancy.

However, even medicines that do not cause any gross physical malformations can cause microscopic defects (such as the vaginal tumors in children of mothers treated with diethylstilboestrol during gestation: Herbst, 1981) or alter the intricate structure or chemical composition of fetal brain tissue to such an extent that permanent behavioral deviations later develop. The latter field, which is known as «behavioral teratology» is the subject of this chapter. Behavioral teratology may not be limited though to effects of chemicals in the second half of pregnancy. For instance, in the autistic syndromes, for which the ethiological factors are not clear at present, the parents were remarkably more often exposed to chemicals in the preconception period than the controls (Coleman, 1979).

1. Substances affecting brain development

Those chemical compounds which are of importance for adult brain function appear in general to be involved in brain development as well (Swaab, 1980). At the present time this principle is established for sex hormones, corticosteroids, thyroid hormones, and neurotransmitters. Substances which alter the balance of any of these compounds during ontogeny are therefore capable of altering the course of brain development in a permanent way.

Sex hormones in the rat, acting during the perinatal period, affect maturation of the brain — both structurally and functionally — in a different way in the two sexes. For example, a light macroscopically evident sexual dimorphism occurs in the size of a part of the nucleus preopticus medialis (the sexual dimorphic nucleus of the preoptic area = SDN-POA), which is determined by the levels of testosterone present around the time of birth (Gorski et al., 1978, Jacobson et al., 1980). An analog of the SDN-POA has recently been described by us in the human brain. The volume of this nucleus is 2.5 times as large in men as it is in women and contains 2.2 times as many cells (Swaab and Fliers, 1985). Sex Hormones coming from the fetus constitute in normal development most probably the biological basis for such sex-related brain and beha-
behavior differences in animals as well as in humans. These differences include not only such obvious phenomena as sexual behavior patterns and the size of related brain structures, but also performance in a variety of learning situations (Van der Poll et al., 1978).

It is therefore a matter of considerable concern that progestatives, estrogens and/or combinations thereof have frequently been prescribed to pregnant women (Reinishch and Karow, 1977), in the mistaken belief that they prevent impending miscarriages. In the United States one to 4.5 million pregnant women used diethylstilboestrol (DES) from 1945 until 1971. It was taken off the market only due to a probable carcinogenic effect on the cervix and vagina in female offspring (Herbst et al., 1981). Not only are these drugs ineffective in sustaining pregnancy, but their use entails a real possibility of inducing personality disorders in the offspring. Estrogen-exposed children have been found between 4 and 21 years of age to be generally less self-confident, less sensitive, and more dependent and group oriented than normal children (Reinishch and Karow, 1977). In addition, a high (25%) percentage of infertility and possible interference with sexual function was found following intruterine exposure to injected estrogens (Stenchever et al., 1981; Beral and Colwell, 1981).

Prenatal administration of estrogen and progesterone in boys has been reported to influence certain aspects of postnatal psychosexual development most noticeably (i.e. 'masculinity', 'aggressiveness', and athletic abilities) (Yalom et al., 1973). It is worth mentioning that sexual differentiation of the brain is not only affected by sex hormones. Similar developmental effects have been described for serotonin, noradrenaline (see below), and dopamine related drugs (Hull et al., 1984), alcohol (McGivern et al., 1984), cimetidine (Anand and Van Thiel, 1982), morphine (Vathy et al., 1983), barbiturates (Reinishch and Sanders, 1982), and maternal stress (Dörner, 1979). Consequently, all types of neuroactive compounds might affect sexual differentiation of the brain.

Corticosteroids are used during pregnancy, for example in cases of allergic reactions, and to promote lung development in the child in cases of imminent parturition (as recommended by Liggins and Howie, 1972). However, in a number of patients this treatment did not seem to have the expected effect (Gariet et al., 1981). In addition, animal experiments indicate that exposure to corticosteroids can retard brain development and affect behavior in later life (Balazs et al., 1975; Taeusch, 1975; Dahlof et al., 1980; Sobel, 1978; Johnson et al., 1981). It has been demonstrated that corticosteroids also affect glial cell proliferation in rat brain (Howard and Benjamin, 1975). Marton et al. (1979) found a slowing of psychomotor development, which persisted at least up to 2 years of life in prematurely born children who had been exposed to corticosteroids. A good prospective study is badly needed in this area.

Thyroidhormones have been injected directly into the amniotic fluid in order to enhance fetal lung maturation (Mashiach et al., 1978). No follow-up investigation of these children has been carried out to our knowledge, although it is known from animal experiments that such treatment may hamper brain development (Balazs, 1979).

Recent research also indicates that neurotransmitters which can be subdivided into the following groups: acetylcholine, biogenic amines, amino acids and peptides are essential for normal brain development.

(1) Acetylcholine. Pyridostigmine (an acetylcholinesterase inhibitor), when administered to neonatal rats, induces premature puberty and increased male sexuality in both sexes of the offspring (Hinz et al., 1978). Nicotine (an acetylcholine receptor agonist) enhances cell death in the rat foetal brain stem (Kraus et al., 1981) while neonatal administration of chlorisodamine (a nicotine-receptor blocker) prevented the normal postnatal increase in volume and cell number of the mouse superior cervical ganglion (Black and Geen, 1974).

(2) Biogenic amines. Apart from the serotonin-reuptake blocker (chlorimipramine) and the alpha-adrenergic agonist (clonidine), see below, there are many examples of drugs which, if used during pregnancy, impair normal brain development by upsetting the balance of the mono-
amines and/or influencing the sensitivity of the receptors. In animal experiments, reserpine (used as an antihypertensive drug as well as a tranquilizer) decreases the monoamine levels in the brain and has been shown to induce permanent brain and behavioral changes in the offspring (Thornburg and Moore, 1976; Hutchings, 1978; Patel et al., 1981; Barlow and Sullivan, 1975). These include reduced formation of neurons, hyperactivity, and increased susceptibility to audiogenic seizures.

Amphetamine, which increases the release of catecholamines in the brain, is commonly used as a dieting aid but is also given to children in cases of enuresis nocturna or minimal brain dysfunction (Huygen, 1979; Hitzemann et al., 1976; Naseklo and Ramirez, 1978; Gross and Wilson, 1974). Offspring of pregnant rats treated with such drugs show behavioral changes, most notably an inability in adulthood to adapt to new surroundings (Hutchings, 1978; Hitzemann et al., 1976). Alpha-methyl-dopa (a false transmitter precursor for noradrenaline) and propanolol (a beta-adrenergic blocker), when taken by the pregnant mother, result in a reduced head circumference in the neonate (Moar et al., 1978; Pruynt al., 1979).

The use of neuroleptics such as chlorpromazine (a dopamine antagonist) during pregnancy has been reported to result in extrapyramidal disturbances in the newborn child (Hill et al., 1966), while in animal experiments it impaired learning ability (reviewed in Barlow and Sullivan, 1975). P-chlorophenylalanine, which blocks serotonin synthesis, affects cell division in regions of the posterior diencephalon known to become innervated by serotonergic fibers (Lauder et al., 1983; Lauder and Krebs, 1984a, b). Barbiturates, which also stimulate dopamine receptors (Yanai and Feigenbaum, 1981), are commonly used as hypnotics, sedatives, anticonvulsives and for preventing neonatal jaundice. They may induce a long-term withdrawal syndrome lasting as much as 3 months (Thornburg and Moore, 1976). In animal studies, barbiturates have been shown to impair reproductive function and maze-learning ability of the offspring despite the absence of obvious CNS deformities (Clemens et al., 1979; Gupta et al., 1980; Middaugh et al., 1975).

(3) The Amino acids. Our present knowledge of the possible effects on brain development of drugs acting upon this group of transmitters is disappointingly small, even though large amounts of sleeping pills and tranquilizers, affecting aminoacid neurotransmitters, are used during pregnancy and postnatal development. According to the newspapers some 950,000 prescriptions for such compounds per year would be given to German children up to the age of 11. It is important to emphasize that almost any disturbance in amino acid metabolism goes together with mental retardation (Lee, 1980).

Prenatal or early postnatal treatment of rats with the often used tranquilizer diazepam which acts upon GABA receptors (Kruck and Pycock, 1979) produces long-lasting effects on brain enzymes, thereby resulting in behavioral disturbances such as hyperactivity and lack of acoustic startle reflexes (Fonseca et al., 1976; Kellogg et al., 1980; Jakoubek, 1978). It also reduces choline uptake in the male rat frontal cortex (Grimm, 1984) and induces alterations in the central and peripheral responses to restrained stress in rat progeny (Simmons et al., 1983). Diazepam administration during pregnancy in humans results in low Apgar scores, depressed respiration and impaired sucking (Cree et al., 1973; Patrick et al., 1972). Long-term follow-ups of such children are lacking.

(4) Peptides. Little is known about the possible long-term effects on brain development of this recently discovered group of neurotransmitters that were originally though to be simply hormones produced by the hypothalamus, e.g. vasopressin, oxytocin, LHRH, TRH and somatostatin, but which later appeared to have important central effects as well (for review see Swaab, 1982).

Oxytocin is routinely used in obstetrics and may cause fetal distress, including a rise in core temperature and possibly retarded motor and speech development. Observations in the rat revealed a permanent decrease in water metabolism following administration of oxytocin to the
developing rat (for references see Boer and Swaab, 1983). It will probably take gynaecologists some time to get used to the idea that even oxytocin can be considered as a neurotransmitter, and thus as a «psychotropic drug» that may, in principle, affect the child by a direct action on the developing brain. Vasopressin, which can permanently alter osmoregulation following perinatal administration (Boer and Swaab, 1983; Boer et al., 1984), and its analogues have been given to mentally retarded children (Eisenberg et al., 1984 a + b; Waggoner et al., 1978; Anderson et al., 1979). Vasotocin administrated to kittens induced delayed eye-opening and brain lipid content while locomotion was diminished and periods of active sleep were enhanced (Goldstein, 1984). Postnatal treatment with TRH increased hypothalamic weight and impaired T-maze learning (Stratton et al., 1976). CRF accelerated eye-opening, enhanced rearing in an open-field and impaired body temperature registration. Substance-P increased pain reception and induced upregulation of its receptors (Handler et al., 1984; Handler, 1985), while neonatal exposure to a high level of ACTH 4—10 impairs adult learning behavior (McGivern et al., in press). Opioids and compounds influencing this system, have strong effects on brain development. Methadone exposure of developing rats caused e.g. a delay in reflex development, eye-opening, somatic- and brain growth, a regional alteration of catecholamines, hyperactivity, increased emotionality, learning disabilities and dysfunction of thermoregulation and nociception. In children whose mothers were exposed to opioids abstinence symptoms were found, a high rate of mortality, sleep disturbances, delays in the sensorimotor development, retardation in somatic growth, smaller head circumference, delays in walking, problems in visual and auditory systems, aberrations in neuroontogeny, less alertness, poor attention spans, hyperactivity, learning disabilities and social problems (Zagon and McLaughlin, 1984). Naloxone, an opiate antagonist, is administered clinically in order to normalize fetal heart rate (Goodlin, 1981). Animal experiments have implicated naloxone as the cause of a permanent impairment of sensitivity to thermal stimuli (Sandman et al., 1979) and of maze-learning ability (Vorhees, 1981). Beta-endorphin, used during delivery as an analgesic (Oyama et al., 1980), induces similar disturbances in the rat (Sandman et al., 1979). This treatment causes a reduced beta-endorphin immunocytochemical staining in various brain regions (Moldow et al., 1981).

2. Mechanisms of action of medicines on the developing brain

Drugs taken by the pregnant mother may impair the developing child’s brain in different ways. (1) The action may be indirect, as in the case of aspirin which, when taken by the pregnant mother, makes the fetus more susceptible to the stress of labor, thus resulting in a higher incidence of intracranial bleeding and perinatal mortality (Rumack et al., 1981; Collins, 1981). Another action of this kind is the alcohol induced impairment of umbilical circulation producing hypoxia and acidosis in the fetus (Mukherje and Hodggen, 1982). Prenatal exposure to barbiturates might also influence brain development indirectly by altering liver metabolism of sex hormones (Reinsch and Sanders, 1982).

(2) Drugs may affect brain development by interacting directly with the formation of the neuronal and glial network, e.g. by affecting cell division, cell death, cell migration, or the formation of neuronal dendrites, synapses and receptors. Most, if not all, medicines in fact appear to affect several of these processes simultaneously.

Cell division is reported to be slowed down by a number of medications, both in vivo and in vitro (Patel et al., 1981). Barbiturates were found e.g. to cause a 30% reduction in the number of cerebellar Purkinje cells and a 15% reduction in hippocampal pyramidal cells (Hutchings, 1978;
ORNoy and Yanai, 1980; Culver and Vernadakis, 1979; Diaz and Schain, 1978). Other compounds which have similar deleterious effects include corticosteroids (DeLemos and Moore, 1976), chlorpromazine (Patel et al., 1980), alcohol (Barnes and Walker, 1981) reserpine (Patel et al., 1981), thyroid hormone (Balazs, 1979) and sex hormones (Gorski et al., 1978; Jakobsen et al., 1980). Indirect evidence for decreased brain cell division is provided by the smaller head circumferences which have been found at birth following treatment with sex hormones (H.J. Huizes, pers. comm.), with alpha-methyl-dopa or propranolol (Moar et al., 1978; Pruyn et al., 1979), and hydantoin (Hanson and Smith, 1976; Hanson, 1978; Hilesma et al., 1981), or by the use of alcohol (Iosub et al., 1981; Quelette and Rosett, 1976) during human pregnancy. Cell death is augmented by nicotine (Kraus et al., 1981) and accelerated by alcohol exposure prior to birth (Yanai, 1981).

Cell migration is disturbed by alcohol (Jones et al., 1976) and monosodiumglutamate (Marani et al., 1982).

The formation of neurites and synapses is known to be affected by sex hormones (Arai et al., 1978; Greenough et al., 1977; Salaman, 1974; Toran-Allerand, 1976), by corticosteroids (Howard and Benjamin, 1975), by morphine/methadone (Hutchings, 1978; Slotkin et al., 1979; Strauss et al., 1979; Kreek, 1979; Kaltenbach et al., 1979), by anticonvulsive agents (Culver and Vernadakis, 1979) and by alcohol (Hammer and Scheibl, 1981; West et al., 1981). Receptors may also be permanently altered by neuroactive compounds given during development. Haloperidol, which blocks dopamine receptors, induced a permanent decrease in the number of dopamine receptors in the striatum (Roessgarten and Friedhoff, 1979). L-dopa, which increases dopamine synthesis, permanently increases receptor density (Friedhoff et al., 1977). Prenatal morphine exposure in the rat increases the adult number and affinity of spinal cord opiate receptors (Kirby, 1984).

Another direct effect of drugs is upon non-neuronal elements in the brain, e.g. the glia cells. There is strong evidence, for instance, that neuroleptic drugs inhibit glial adenylate cyclase activity (Henn, 1982), while corticosteroids probably affect glial cell proliferation (Howard and Benjamin, 1975). Clonidine interacts with glial cells by decreasing their cyclic AMP level (Henn, 1982).

(3) The third mechanism involves effects of medicines on spontaneous behavioral states, namely wakefulness, quiet sleep and rapid eye movement sleep. Although behavioral states are readily influenced by a majority of the commonly used medicines, little attention has been paid to this fact in most of the literature dealing with behavioral teratogenicity. Since behavioral states are generated exclusively in the brain, monitoring physiological characteristics of these spontaneous behaviors during development is the most sensitive indicator of the influence of drugs on fetal brain functions.

In a study at our institute in which the long-term effect of REM sleep (active sleep: AS) deprivation on brain and behavior development was studied, experimental suppression of AS during early postnatal life by means of clomipramine or clonidine in rats, revealed a clearcut reduction of cortical size, higher level of open field activity, deficient masculine sexual behavior, and disturbed sleep patterns in adulthood (Mirmiran et al., 1981; Mirmiran et al., 1983a; Swaab and Mirmiran, 1984). These results, and those of others using different pharmacological as well as non-pharmacological approaches, argue in favor of AS as being a mediating factor for normal brain maturation (Juvancs and Nowaczky, 1975; Mittler, 1971; Saucier and Astic, 1975). The specific reduction of cortical weight, together with decreased protein content, in the absence of any significant change in cell number, was highly reminiscent of the picture seen in rats reared under sensorially impoverished conditions (Rosenzweig and Bennett, 1978). This similarity suggested that the developmental effects of rearing in «enriched» environments may entail an interaction between AS and experimental «traces» laid down earlier during periods of
wakefulness. This hypothesis is rendered still more credible by the demonstration that the amount of AS increases during enrichment rearing (Mirmiran et al., 1982).

Furthermore, concomitant AS-deprivation by means of clonidine neutralizes the effect that environmental enrichment normally exerts upon cortical growth (Mirmiran and Uylings, 1983 b).

Another intriguing finding is that prolonged AS-deprivation by means of clonidine even prior to the period of enrichment rearing interferes with the expected extra brain growth (Mirmiran et al., 1983 b). Apparently, cortical mechanisms underlying «plasticity» in later life can be adversely affected by the absence of AS and/or noradrenaline disturbances in early development. Such a phenomenon may implicate abnormal sleep patterns in development as a potential contributory factor to learning deficiencies in humans as well.

The drugs used in the AS-deprivation studies, viz. clomipramine (Anafranil) and clonidine (Catapresan) are also used in clinical practice (for treating depression, hypertension, migraine, nocturnal enuresis, sleep apnea, opiate withdrawal, minimal brain dysfunction etc.). The potential seriousness of such exposure has already been emphasized by Monod of the University of Paris, who discontinued clomipramine treatment in infants up to 3 months of age suffering from sleep apnea (pers. comm.), after learning about these animals' experimental results (Mirmiran et al., 1980).

A recent follow-up study examined the effects of prenatal clonidine treatment of hypertensive mothers on the development of children that are now 6—8 years of age. In the exposed group compared to non-treated hypertensives an excess of anxiousness and sleep disturbances was found together with a trend towards an increased incidence of hypotonia. (Huisjes et al., 1985).

3. Clinical awareness required

A wide variety of chemical compounds having comparable effects upon monoamine systems and/or AS are currently in clinical use. It is both surprising and a source of concern that practically no follow-up studies appear to have been carried out on the possible long-lasting functional consequences of such treatments in man. Table 1 lists the most commonly used drugs during the prenatal and early postnatal periods. Some of these substances have demonstrable teratogenic effects, and almost all of them tend to suppress AS.

It is important to point out that almost all the drugs used during gestation easily cross the placenta, and their level in the fetus (especially in the brain) is even higher than in the maternal circulation (Mirkin and Singh, 1976). In addition, humans are often more sensitive than animals to teratogenicity of drugs (Council of Environmental Quality, 1981). The offspring of many drug-addicted mothers exhibit withdrawal symptoms (Hill and Stern, 1979). The possibility of fetal sleep disturbances during gestation as well as during the withdrawal period has been ignored so far. However, one report does demonstrate a prolonged disturbance of sleep in babies born from heroin-addicted mothers (David and Glass, 1980). A similar mechanism might be responsible for the smaller head circumferences in boys, up to 4 years of age, born to mothers treated with alpha-methyl-dopa during late gestation (Moar et al., 1978; Unsted et al., 1980). The sleep disturbances found in children whose mothers used clonidine during pregnancy indicates that animal experimental studies might allow a selection of the right functions to study in human follow-ups (see before). Long-term follow-up without a strong indication as to which behaviours or functions should be studied in later life will most probably fail to find any disturbances.

The direct and indirect effects of a variety of clinically used drugs upon the development of the
brain have been reviewed here. Taken together, the literature on this subject points to a potential health hazard not only during the first trimester of pregnancy (as is now generally accepted) but also throughout the entire period of gestation, and even during lactation. Obstetricians, neonatologists, and pediatricians should, therefore, be aware of the fact that the immediate beneficial effects of many drugs may be offset by the induction of permanent behavioral and psychological defects within the children's developing brains. This is an especially relevant consideration in cases involving children suffering from minimal brain dysfunction who are often subjected to extremely high doses of imipramine- or amphetamine-like drugs (for review see Gross and Wilson, 1974) despite the fact that improvement often occurs eventually even in the absence of any medication whatsoever. The same point can be made, of course, for the treatment of nocturnal enuresis and sleep apnea by means of antidepressants. It is an unfortunate commentary at the present time that the mothers themselves are often more aware of the potential dangers inherent in the use of medicines during pregnancy than are the physicians who prescribe them. We suggest that the investigation of the link between experimental and clinical medicine in this area, viz. the question of behavioral teratologic sequelae of medications administered during early development, ought to be encouraged (Swaab, 1985; Swaab and Mirmiran, 1985).

Acknowledgements

We are grateful to Mrs W. Cohen-Pelt for her secretarial help.

Tab. 1: Sequelae of chronic drug exposure during gestation, labor, lactation and childhood in man and other mammals.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Brain and behavioral teratogenicity in man</th>
<th>Brain and behavioral teratogenicity in animals</th>
<th>AS-deprivation effect</th>
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<td><strong>Antihypertensives</strong></td>
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<td>α-Methyl-dopa</td>
<td>Questionable neurological status, smaller head circumference (Moar et al., 1978)</td>
<td>Hyperactivity and delayed motor coordination (Saucier and Astic, 1975)</td>
<td><strong>Saucier and Astic, 1975</strong></td>
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<td></td>
<td>Delayed visual motor performance, smaller head circumference (ounsied et al., 1980)</td>
<td>Hyperactivity (Juvancs and Nowaczyk, 1975)</td>
<td><strong>Valatx and Nowaczyk, 1977</strong></td>
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<td>Propanolol</td>
<td>Light for dates, smaller head circumference, bradycardia (pruynt et al., 1979)</td>
<td>Reduced brain weight and brain/body weight ratios (Grant and Samson, 1984)</td>
<td><strong>Lanfumeys and Adrien, 1981</strong></td>
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<td></td>
<td>Prolonged labor, neonatal respiratory depression, bradycardia (habib and McCarthy, 1977)</td>
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<td>Reserpine</td>
<td>Anorexia, lethargy (Yaffe and Stern, 1976)</td>
<td>Reduced brain cell proliferation (Patel et al., 1981)</td>
<td><strong>Hoffman and Domino, 1969</strong></td>
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<tr>
<td>Clonidine (also used for migraine, in opiate withdrawal and for depression)</td>
<td>Anxious, sleep disturbances (huisjes et al., 1985)</td>
<td>Increased anxiety, reduced masculine sexual behavior smaller brain (Mirmiran et al., 1983 a)</td>
<td><strong>Autret et al., 1977</strong></td>
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<td><strong>Kleijnlogel et al., 1975</strong></td>
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<td><strong>Miettinen, 1981</strong></td>
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<td>Drugs</td>
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<td>Anticonvulsants and hypnosedatives</td>
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<td>Reduced responsiveness to sensory stimuli (BRAZELTON, 1970)</td>
<td>Increased locomotion in openfield, decreased acquisition in passive avoidance, less response to environmental stimuli (MIDDAUGH et al., 1975) Reduced brain weight; destroys already formed neurons; impairment of learning (YANAI, 1980)</td>
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<td>Hydantoin</td>
<td>Low IQ scores (HANSON and SMITH, 1975) Microcephaly, mental retardation (HANSON, 1978) Smaller head circumference, mental deficiency (IQ &lt; 85) (HANSON et al., 1976) 2−3 times higher rate of mental retardation (Amer. Acad. Pediat.; Committee on Drugs, 1979) Smaller head circumference (HILESMA et al., 1981; OGAWA et al., 1982; for review see BOSS, 1982)</td>
<td>No data available, but see Reduced brain weight as a result of chronic Dipropylacetate (DIAZ and SHIELDS, 1981)</td>
<td>COHEN et al., 1968</td>
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<td>ACTH</td>
<td>Apathy, drowsiness, pseudodementia (LANGENSTEIN et al., 1979)</td>
<td>Accelerates the onset of eye opening and motor behavior (SWAAB and MARTIN, 1981)</td>
<td>GILLIN et al., 1974</td>
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<td>Tranquilizers</td>
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<td>Diazepam</td>
<td>Low Apgar scores, reluctance to eat (GREE et al., 1973) Lethargy, impaired suckling (PATRICK et al., 1972) Depressed reflexes (MCCARTHY et al., 1973)</td>
<td>Increased locomotion and decreased defecation in males; lower performance in maze learning (FONSECA et al., 1976) Lack of acoustic startle reflexes (KELLOG et al., 1980) Sleep disturbances and reduced diazepam-specific receptor bindings (LIVEZAY et al., 1985)</td>
<td>KALES and SCHARF, 1973</td>
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<td>(It has also been used to prevent premature labor (FUCHS, 1965)</td>
<td>Low Apgar and high incidence of respiratory distress (ZERVOUDAKIS, 1980)</td>
<td>Destroys already formed neurons; depression of aggressive behavior; impairment of learning (YANAI, 1981)</td>
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<td>Amphetamine</td>
<td>Withdrawal symptoms (HILL and STERN, 1979)</td>
<td>Marked reduction in ability to habituate to new surroundings (NASELLO and RAMIREZ, 1978)</td>
<td>RECHTSCHAFFEN and MARON, 1964</td>
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<td>Corticosteroids (in addition used in pregnant women for infertility and subsequent maintenance of pregnancy)</td>
<td>No data available</td>
<td>Cell proliferation ceases prematurely throughout the brain (BALAZS, 1979)</td>
<td>DUNLEAVY et al., 1974</td>
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<td>Thyroxine</td>
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<td>(MASHIACH et al., 1978; WU et al., 1973)</td>
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<td>Antidepressants</td>
<td>Poor suckling, irritability, urinary retention, breathlessness, tachypnoea, cyanosis (HILL and STERN, 1979)</td>
<td>Increased emotionality, decreased masculine sexual behavior, smaller brain and cortical size (MIRMIRAN et al., 1983) a RODRIGUEZ ECHANDIA and BRAITMAN, 1983)</td>
<td>SHIMIZU and HIMWICH, 1969</td>
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<td>Imipramine-like compounds</td>
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<td>MIRMIRAN et al., 1981</td>
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<td>Neuroleptics</td>
<td>Extrapyrpyramidal dysfunction (e.g. tremor, hypertonus, etc.) (HILL et al., 1966)</td>
<td>Reduction in brain DNA contents (PATEL et al., 1980; VERTES et al., 1980) Impairment of maze learning and reduction of exploratory behavior (HOFFELT and WEBSTER, 1965)</td>
<td>KHAZAN et al., 1967</td>
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<td>Chlorpromazine</td>
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Drugs | Brain and behavioral teratogenicity in man | Brain and behavioral teratogenicity in animals | AS-deprivation effect
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**Prevention of abortion**

**Estrogen**

- Decrease independency, sensitivity, self-assurance *(REINISCH, 1977)*
- Decrease «masculinity», aggressiveness and athletic ability *(YALOW et al., 1973)*
- Lower proportion of marriage *(BERAL and COLWELL, 1981)*
- Smaller head circumference *(H.J. HUISJES, pers. comm.)*

- Increased locomotion and impaired maze learning *(FONSECA et al., 1976)*
- Effects upon various behaviors depending upon the dosage used and the sex of the animals *(BRANCHEY et al., 1971)*

**References**


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