Effects of perinatal medication on the developing brain

M. MIRMI Ran and D. F. SWA AB

During the third trimester of pregnancy the brain of the fetus is able to display complex neurobehavioral functions. At the same time this rapidly developing brain is very susceptible to chemicals used by the mother. In addition to self-medication, there is widespread (80 per cent) drug administration to pregnant and lactating women for the treatment of, for example, hypertension, epilepsy, depression, and premature labour (Eskes et al. 1983). Disturbances caused by such chemicals used during the third trimester are not usually of a grossly physical nature, but are based upon permanent microscopic and biochemical alterations in the formation of neurones, their migration, formation of neurites, synapses, transmitters, receptors, and behavioral states. The effect of functional deficits induced in the child in this way is called behavioral teratogenicity, or rather functional neuroteratology, since neuroendocrine systems or temperature regulation, for example, may be affected. This topic has recently received much attention and its potentiality has been reviewed in a volume of the series of Progress in Brain Research (Boer et al. 1988). The intention of this chapter is to update our knowledge of the subtle changes induced in the developing brain of the unborn child by drugs used during the last trimester of gestation. We limit ourselves to the sequelae of a number of drugs, and for further reading on this topic we refer to earlier reviews (Benesova 1989; Eskes and Finster 1983; Hutchings 1978; Mirmiran and De Boer 1988; Mirmiran and Swaab 1987; Riley and Vorhees 1986; Swaab and Mirmiran 1984, 1988; Swaab et al. 1988; Yanai 1984). We want especially to point out the sensitivity of man to the hazards of medicines and to put forward the hypothesis that neurotransmitter, neuroendocrine, and behavioral state changes in response to drugs may indeed mediate the occurrence of a macroscopically normal but functionally handicapped brain.

Effects of drugs on brain neurotransmitters

Monoamines (i.e. noradrenaline (NA), serotonin (5HT), and dopamine
(DA)) are among the best-studied brain neurotransmitters. Rats, the experimental animal model generally used for behavioural teratology experiments, are very immature when born. For example, the cerebral cortex of a newborn rat is comparable to that of a 7-month-old human fetal brain (Dobbing and Sands 1979), although this might not always be a good comparison (see later). In the rat, which has a gestational period of about 21 days, NA, DA, and 5HT neurones are already born and functionally responsive to pharmacological manipulations by day 15 of gestation (Lauder and Bloom 1974; Mirmiran 1986; Mirmiran et al. 1988). An early appearance of monoamines has been shown by mid-term in the human fetus (Hyppä 1972; Masudi and Gilmore 1983; Nobin and Björklund 1973; Olson et al. 1973; Pearson 1983; Pearson et al. 1980). A similar early development of neurotransmitters in fetal human brain has been shown for other neurotransmitters: e.g. acetylcholine, by as early as 18 weeks of gestation (Brooksbank et al. 1978; Schlumpf and Lichtensteiger 1987); amino acids as early as mid-gestation (Brooksbank et al. 1981; Repressa et al. 1989); and a variety of peptides before mid-gestation (Aubert 1979: Bloch et al. 1978; Bugnon et al. 1977; Paulin et al. 1986; Siler-Khodr and Khodr 1978; Winters et al. 1974). However, there are two factors to bear in mind. First there are considerable regional differences in the developmental time of each given neurotransmitter in the brain. Secondly, although in a particular period of development an excess of a neurotransmitter may be trophic for the maturation of a certain brain area, in an earlier period it may be insensitive, or in a later period toxic, to the maturation or survival of the neurones (Balázs et al. 1989).

In order to demonstrate the functional capacity and sensitivity of the monoaminergic neurons to drugs in the developing brain, several biochemical and electrophysiological studies have been carried out in rats. Drugs such as reserpine, alpha-methyldopa, and clonidine, which are used for the treatment of hypertension, upset the balance of the monoamine levels and/or influence the sensitivity of the receptors as effectively in fetal and newborn rats as in adults (Feenstra et al. 1991; Nomura et al. 1982; Tennyson et al. 1983). Another antihypertensive drug, propranolol, significantly reduced NA content and turnover in the brain of the developing rat when administered from day 1 to 21 postnatally (Erdstieck-Fürnste et al. 1991). Feenstra et al. have shown that clonidine is as effective in reducing the amount of NA activity in many brain areas of the rat throughout development as it is in adulthood (Boer et al. 1990). Tricyclic antidepressants, such as imipramine and clomipramine, inhibit the re-uptake of both NA and 5HT in the developing brain to the same extent as in adulthood (Nomura et al. 1978).

Animal studies have indeed improved our knowledge of neurotransmitter disturbances as one of the mechanisms of the neuroteratological
disturbances induced by chemicals. Such systematic, well-controlled, developmental studies on drug administration can not of course be carried out in humans. However, in the near future some parameters of neurotransmitter activity may be sought in humans, for example the content of neurotransmitters and their breakdown products in the cerebrospinal fluid, receptor binding studies using blood platelet or placental tissue, PT scan and NMR techniques, and—if brain material is available—immuno-cytological and biochemical studies. Recent studies by Perry et al. (1984), and Perry (1988) using human placental tissues have strengthened the hypothesis that prenatal drug exposure in man may result in neurotransmitter system changes, which in turn, cause behavioural teratology. On the assumption that placental tissue neurotransmitter regulation may mirror fetal brain receptor regulation, placental neurotransmitter receptors from opioid-drug-abusing pregnant women and controls have been examined by these investigators. Increased amounts of opiate receptors and adrenergic receptors were found in the placentas of women who had used opiates and amphetamines during gestation.

Effects of drugs on behavioural states

Behavioural sleep–wake states of the fetus are manifest by the third trimester of pregnancy (see Chapter 3). Fetal behavioural states are: state 1F (quiet sleep); state 2F (rapid eye movement (REM) sleep); state 3F (quiet wakefulness); and state 4F (active wakefulness). Since the behavioural states are generated in the brain and show a very close relationship to the stage of brain development, they may be used as a good indicator of chemical hazards to the brain. Unfortunately, so far the effects of only a few drugs on behavioural states during development have been tested, and mainly following drug withdrawal (Hutchings et al. 1979). Our own studies have shown clear disturbances of sleep–wake patterns during chronic administration of antidepressant drugs, such as clomipramine or antihypertensives, such as clonidine or alpha-methylldopa, in the developing rat (Mirmiran 1986; Mirmiran et al. 1981, 1983a, 1985). Chronic administration of each of these drugs to developing rats dramatically reduced the amount of time spent in state 2, as well as the amount of eye movement during this state. Similar results were found by other investigators (Hilakivi et al. 1988; Vogel et al. 1990).

Although ultrasound techniques are frequently used in clinics, very few studies have attempted to investigate systematically the influence of drugs used by pregnant women on fetal behaviour during chronic exposure. Such tests would yield very straightforward evidence of the amount of functional damage inflicted on the fetal brain as a result of maternal medication. In a
study by Arduini et al. (1987) a clear-cut reduction of fetal states 1 and 2 was found on naloxone administration to pregnant women near term. In an ongoing study by the group of van Geijn at the Free University of Amsterdam, changes in fetal behavioural states were found in women treated with anti-epileptics.

Most drugs easily pass the placenta and fetal blood–brain barrier, and their concentration in the fetal brain may be much higher than in the maternal plasma (Mirmiran and Swaab 1987; Mirmiran et al. 1985). The majority of these compounds suppress state 2 and disturb the normal sleep–wake cycle rhythms (Swaab and Mirmiran 1984). There are drugs that influence sleep by affecting different brain neurotransmitters, such as NA (e.g. alpha-methyldopa, clonidine, and propranolol), 5HT (e.g. imipramine, clomipramine, and imipramine), and gamma-aminobutyric acid (e.g. diazepam). Several investigators have examined behavioural states of passively-dependent human infants during opiate withdrawal. A significant decrease in state 1 was found in neonates prenatally exposed to opiates, and this profile is shared by many neonates with a high risk of central nervous system impairment (Dinges et al. 1980; Schulman 1969). A decrease in both state 1 and 2 was found in the neonates of addicted women (Sisson et al. 1974). Sisson et al. concluded that since protein synthesis is stimulated during state 2, withdrawal treatment may be essential not only to relieve the symptoms, but also to promote normal and necessary sleep patterns required for brain development (Mirmiran et al. 1983a).

Long-term consequences

Animal studies

We have studied the long-lasting effects of several drugs chronically administered to the developing rat, at biochemical and electrophysiological levels in adult animals (Boer et al. 1990; Gorter et al. 1989; Mirmiran et al. 1985, 1988, 1990). Clonidine reduced NA turnover in the adult brain of neonatally-treated rats. In the hippocampus we found a supersensitivity of the pyramidal neurones to the depressive effects of NA, whereas the cortical neurones were more inhibited by GABA, compared to the controls. Long-lasting changes in rats after perinatal exposure to antidepressants were also reported by Del Rio et al. (1988). These changes include a decreased number of NA and 5HT receptors following perinatal exposure to chlorimipramine, imiprindole, mianserin, and nomifensine during the second half of gestation in rats. Similar brain monoamine disturbances were also reported by Hilakivi et al. (1988).
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Brain and behavioural alterations in man</th>
<th>Brain and behavioural alterations in other mammals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-methyldopa</td>
<td>Smaller head circumference, questionable neurological status, increased myoclonic jerks during sleep</td>
<td>Hyperactivity, delayed motor coordination, hyperanxiety in novel environment</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Smaller head circumference, light for date</td>
<td>Reduced brain weight and brain body-weight ratio</td>
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<tr>
<td>Clonidine</td>
<td>Increased myoclonic jerks during sleep, hypotonia, hyperanxiety, minor neurological dysfunction</td>
<td>Supersensitivity of hippocampal neurons to noradrenaline, reduced level of hippocampal plasticity</td>
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<td>Barbiturates</td>
<td>Hyperactivity, restlessness, disturbed sleep, hyperreflexia, reduced responsiveness to sensory stimuli</td>
<td>Hyperactivity, hyperanxiety, reduced masculine sexual behaviour, impairment of learning, reduced responsiveness to sensory stimuli, smaller brain</td>
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<tr>
<td>Reserpine</td>
<td>Anorexia, lethargy</td>
<td>Smaller brain</td>
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<tr>
<td>Diazepam</td>
<td>Low Apgar, reluctance to eat</td>
<td>Hyperactivity, learning impairment, reduced acoustic startle reflex</td>
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<tr>
<td>Imipramine-like compounds</td>
<td>Poor suckling, irritability</td>
<td>Hyperactivity, hyperanxiety, reduced masculine sexual behaviour, increased voluntary alcohol consumption, smaller brain</td>
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<tr>
<td>Chlorpromazine</td>
<td>Extrapyramidal dysfunction, tremor, hypertonus</td>
<td>Hyperactivity, reduced exploratory behaviour, learning impairment, smaller brain</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Withdrawal symptoms</td>
<td>Marked reduction in ability to habituate to new surroundings, reduction of dendritic spines and dendritic arborization of cortical neurons</td>
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Not only in development, but also in adulthood behavioural states are affected by drugs administered during rapid brain maturation. Developing rats treated with either clomipramine or clonidine show a high level of myoclonic jerks during state 2, as well as disturbances in sleep–wake cyclicity as adults (de Boer et al. 1989; Mirmiran et al. 1981, 1983a; Vogel et al. 1990). Following six days of valium exposure during the last week of gestation, mature prenatally exposed rats displayed significantly less quiet sleep at four months of age than controls (Livezey et al. 1985). Furthermore, the amplitude of circadian rhythmicity of sleep and wakefulness was also reduced. It is interesting to note that the amplitude of the circadian rhythm of maternal body temperature, and thereby that of the fetus, is significantly reduced in genetically hypertensive rats treated with clonidine during gestation. Moreover, male sexual behaviour was impaired while emotionality was increased in neonatally chlorimipramine- or clonidine-treated animals (Mirmiran et al. 1981, 1983; Vogel 1990). Neonatal treatment with clomipramine or clonidine reduced the size of the brain studied in adulthood (Mirmiran et al. 1983a). On the other hand, brain plasticity, measured either by environmental stimulation, or by electrical stimulation of the hippocampus, was reduced in clonidine-treated rats (Gorter et al. 1990; Mirmiran et al. 1983b; Nelson et al. 1985). Similar impairment of brain plasticity in response to environmental novelty was reported earlier by Coyle and Singer (1975) in rats prenatally exposed to imipramine.

**Human studies**

Human studies on the long-term consequences of drug use during pregnancy on the development of the child are rare. Nevertheless there are certain data suggesting similar deleterious drug effects as found in animal studies (Table 10.1; Mirmiran et al. 1985; Swaab and Mirmiran 1984; Swaab et al. 1988). Prenatal exposure of hypertensive pregnant women to alpha-methylldopa causes smaller head circumference, minor neurological dysfunctions, and increased myoclonic jerks during sleep in the child (Shimohira et al. 1986). Propranolol also causes a smaller head circumference and a higher incidence of babies who are smaller than average for their gestational age (i.e., small gestational age, SGA). Prenatal exposure to clonidine does not cause smaller head circumference, but it does lead to sustained hypertension in the neonate during the first three days of life (Boutroy et al. 1988), increased myoclonic jerks during sleep, and enhanced sleep terrors in children of 3 to 9 years of age (Huisjes 1988; Huisjes et al. 1986). Hadders-Algra et al. (1986) of the Groningen prenatal group have carefully studied the physical, neurological, and behavioural development of a large group (n=78) of 6-year-old children who were prenatally exposed to ritodrine. No neurological differences were found between the ritodrine and the control group.
However, all of the drug-exposed children showed inferior school performance in motor and social skills, emotional development, and cognitive development. Drugs such as barbiturates induce withdrawal symptoms in neonates, for example hyperactivity, restlessness, disturbed sleep, hyperreflexia, and reduced responsiveness to sensory stimuli. A recent study by Dessens et al. (unpublished observation) at the Academic Medical Centre of the University of Amsterdam demonstrated that the children of epileptic women had a smaller head circumference due to barbiturate exposure during pregnancy. Diazepam exposure results in neonates with a low Apgar score, hypotonia, and poor suckling. No follow-up studies were carried out in children prenatally exposed to tricyclic antidepressants, although poor suckling and irritability are reported in these children at birth.

Concluding remarks

Some data on functional teratology of drugs used during human gestation certainly point to deleterious effects such drugs might have at the neurobehavioural level, in a manner similar to that observed in animal experiments. However, the available data on humans are scarce. There are also certain problems with respect to applying animal (particularly rat) data to humans (Swaab et al. 1988). In the first place there is no good animal model for humans taking into account the degree of human vulnerability, a comparable stage of brain development at the moment of birth, etc. Although, in contrast to what is generally believed, humans are often more sensitive than animals to the teratogenicity of drugs (Council on Environmental Quality 1981), there are certain unexpected observations. For example a single injection of glucocorticoids to neonatal rats induces adulthood behavioural abnormalities such as hyperactivity, stereotypy, emotional hyperactivity, decreased adaptability, motor incoordination, and impaired reproductive functions (Benesova 1989; Benesova and Pavlik 1989). Moreover, this single injection of glucocorticoid resulted in morphological and biochemical alterations of the brain, reduced cerebellar and hippocampal size, and decreased NA in the hypothalamus. On the other hand, in follow-up studies on premature babies treated with glucocorticoids for the prevention of lung disorders, no significant differences in the medical history or psychological/neurological development of these infants were found compared to non-treated controls (Schmand et al. 1990; Smolders-de Haas et al. 1990); it should be noted that prenatal infusion of dexamethasone in monkeys disturbs the circadian rhythms of maternal uterine activity as well as the fetal hormonal rhythms (Ducsay et al. 1983). However, prenatal exposure to antihypertensive drugs such as clonidine might make the child susceptible to developing hypertension or sleep

Secondly, the drugs are administered to healthy animals, while in the human situation, except in the case of addicted women, they are prescribed to pregnant women with disorders such as epilepsy, hypertension, and depression. Although there are exceptions, a study of continuous clonidine infusion to pregnant hypertensive rats has shown a clear reduction of the amplitude of circadian rhythms of body temperature in the mother. As it is known that the maternal circadian rhythm is one of the main factors in the generation of fetal circadian rhythms (see Part 2), one might expect to see a deleterious effect of drug therapy on the fetus under pathological conditions comparable to those of the human. In general, we do not know exactly to what extent disorder, treatment, and a combination of the two, affect the developing brain of the unborn child.

Huisjes reviewed the problems of studying functional teratogenicity in man (Huisjes 1988). He pointed out a number of important issues to be considered. On the one hand, although structural defects in man can be recognized within one year after birth, recognition of neurobehavioural abnormalities may require a follow-up study of more than 10 years. One of the main problems of recognizing symptoms of functional teratology is the long time interval between the moment when chemicals act upon the developing brain and the occurrence of symptoms. Furthermore, although morphological defects can be identified on the basis of known normal morphology, a description of what constitutes normal neurobehavioural function in an individual cannot always be given. Another important issue is the phase of gestation in which drugs may induce neurobehavioural teratogenicity. While the first trimester of gestation is considered to be more associated with gross morphological abnormalities, the third trimester may be closely associated with functional teratogenicity, since this is the period of rapid growth of the brain. However, it is sometimes hard to find cases in which the drug is administered during only one phase of gestation and not throughout this period, even often including the lactation period. Literature suggests that at present there is not only a potential health hazard of chemicals during the second half of gestation, but during lactation as well, (e.g. PCPs; Schardein 1985). This is also important in relation to the increasing amounts of chemicals prescribed during lactation. The other important point Huisjes makes is that of the consequences for clinical practice when a drug, such as clonidine or ritodrine, is proven to be functionally teratogenic. Should the drug then be replaced by another one of which often nothing is known concerning functional teratology, and which may thus have even worse effects? Should we suspend the treatment and take the risk of the deleterious effects of the disease on the child and mother–child interaction?
These are important questions for which we do not have convincing answers as long as chemicals that have to be given sometimes during gestation have not been studied systematically for functional teratology in man. Only then can we make up the balance between the possible beneficial and detrimental effects of a compound. What we can conclude at present is, therefore, that studies on the functional teratogenicity of drugs used during the second half of gestation should be performed systematically in humans. In such studies the results obtained in animals can be used as guidelines of what to look for (Swaab et al. 1988). This requires a multidisciplinary type of research including both neuroscientists and clinicians, focusing on human research, since we believe that there is in fact only one good animal model for human development, and that is human.

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