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Neurochemical and Electrophysiological Disturbances Mediate Developmental Behavioral Alterations Produced by Medicines

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MIRMIRAN, M., E. BRENNER, J. VAN DER GUGTEN AND D. F. SWAAB. *Neurochemical and electrophysiological disturbances mediate developmental behavioral alterations produced by medicines.* NEUROBEHAV TOXICOL TERATOL 7(6) 677–683, 1985.—Many centrally acting drugs which are prescribed for hypertension, depression, epilepsy, insomnia and asthma may also affect fetal brain neurotransmission and behavioral states. Nearly all these drugs enter the fetal circulation following maternal administration. The immaturity of the blood-brain barrier and greater accumulation in the developing brain make the fetal brain a major target of its mother's medication. Adverse effects that are seen in the fetus are not necessarily evident in its mother. We have shown that drugs like clonidine (an antihypertensive) and clomipramine (an antidepressant), which act on noradrenaline and serotonin neurotransmission in the brain, suppress rapid eye movement sleep in the developing rat. In adulthood, the neonatally treated rats showed hyperactivity, hyperanxiety, reduced sexual behavior, disturbed sleep patterns and reduced cerebral cortical size. Furthermore, such treatment induced an increase in voluntary alcohol consumption and a decreased adaptability of responses to changes in water deprivation in a Y-maze. Little is known about long-lasting consequences of centrally acting drugs used during late gestation in humans. Minor neurological disturbances, such as delayed visual motor performance, smaller head circumference, increased anxiety and disturbed sleep-wake patterns, have been reported in children born to hypertensive mothers treated with clonidine or alpha-methyl-dopa.

Monoamines Rapid eye movement sleep Centrally acting drugs Brain development

THE behavioral teratogenicity of many centrally acting drugs that are commonly used during pregnancy in humans has been investigated by means of monitoring the behavioral repertoire of experimental animals after termination of the treatment [2, 8, 13, 33]; these tests have been carried out either when the animals were still young or as adults. Parallel epidemiological studies have also been done in humans to supplement the animal studies. Of course, such an assay will give an indication of the hazards of such drugs for human development (as in the case of thalidomide), but will not bring us any closer to understanding the mechanisms underlying it. Another difficulty with such studies is that the influence of the drug on development should be rather strong to be detected by the conventional behavioral tests in adulthood.

In the present paper we will describe neurochemical and electrophysiological changes induced by centrally acting drugs during development, keeping in mind that the mechanism of action of most of these drugs is through brain neurotransmitter systems. We wish to emphasize the fact that behavioral and physiological changes in the fetal brain which take place during drug administration are often neglected in teratological studies. We will describe the influences of a few centrally acting drugs (in particular those which act on monoamines) and will attempt to introduce the approach rather than to review the outcomes of different drugs. This approach is important since many centrally acting (psychoative) drugs which are used during pregnancy in humans have been tested for possible teratological effects in animals. We emphasize the fact that an unborn brain is more vulnerable than that of adults, and that its physiology and chemistry as well as the animal's behavioral repertoire are chronically influenced while the treatment continues in ways that are not necessarily comparable to the effects on the mother.

As far as behavioral influences in immature animals are concerned, it is generally admitted that they are not stable and reproducible measures, so that they have often been disregarded. We will show that spontaneously generated behavior can be very sensitive to drug treatment and can even indicate the severity of the treatment effects. We have used the newborn rat as an experimental animal model, although extrapolating results from rats to humans should always be done with some reservations. The rat is an altricial mammal, which is born very immature. A newborn rat is comparable

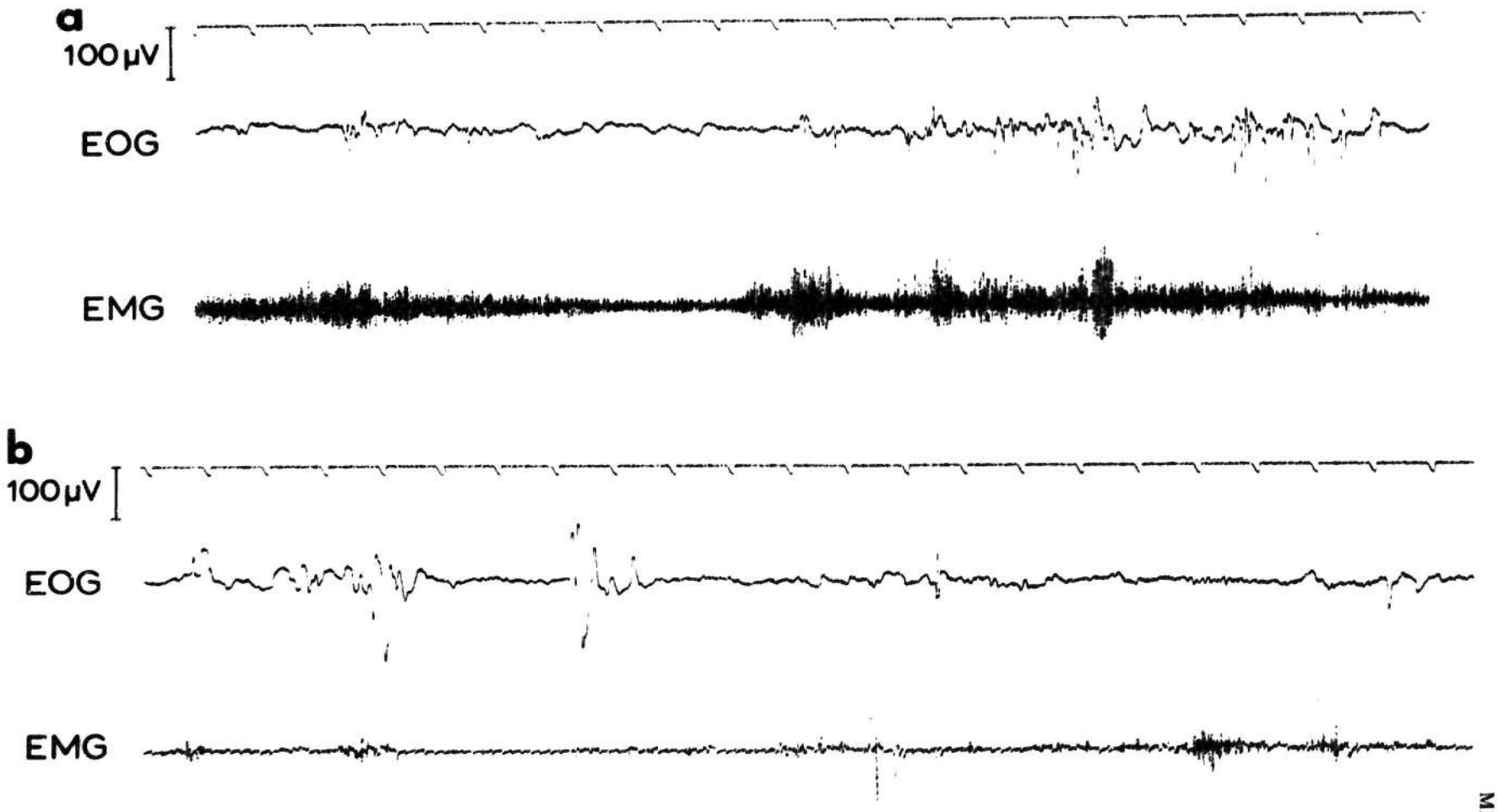

FIG. 1.(a) A representative waking epoch in a 2-day-old rat. (b) A representative REM epoch in the same rat. EOG: electrooculogram; EMG: electromyogram. Time indicated in seconds on the top.

TABLE 1

DEVELOPMENT OF REM (AS PERCENTAGE OF TOTAL SLEEP TIME: REM/TST) AND WAKEFULNESS (AS PERCENTAGE OF TOTAL RECORDING TIME: W/TRT) IN CHRONICALLY SALINE AND CLONIDINE TREATED RAT PUPS

		Age (days)						
		8	10	12	14	16	18	20
REM/TST	Sal	95(2)	81(11)	69 (5)	57 (7)	36 (8)	17 (4)	22(5)
	Clo	15(8)	1 (1)	0	1 (1)	0	0	0
W/TRT	Sal	25(4)	27(11)	41 (4)	56(13)	48(10)	52(10)	57(2)
	Clo	66(3)	47 (9)	55(10)	53 (6)	47 (9)	66 (4)	63(6)

Data shown are mean (SEM) of 3–5 polygraphic recordings in each age group.

to a 7 months human fetus from various structural and functional aspects of brain development [5]. This animal model, therefore, allows us to model human fetal life in an ex-utero animal. Another advantage is that the rat develops very fast, thus limiting the period of observations in any kind of developmental studies.

Behavioral States in Developing Rats: Influence of Drugs

A brief observation of a newborn rat leaves one wondering at the rapid alternation of two distinct behavioral states. One state is characterized by gross, more or less coordinated motor activity including: head raising, head shaking, nipple searching, and rhythmic fore- and hind-paw movements. This behavior is called wakefulness [W], although the eyes are sealed up to about 14 days of age, so that eye opening cannot accompany waking behavior in the infant rat. The second type of behavior, called rapid eye movement sleep [REM], is characterized by a recumbent position, frequent myoclonic jerks and twitches, and eye movements. Combining behavioral and electrophysiological observations in this stage of development can help one to distinguish between these two types of behavior. Using fine microelectrodes (100 μ = nichrom wires) inserted into the dorsal neck muscles or placed subcutaneously at both sides of one eye ball, one can easily record electrophysiological signals in chronically implanted newborn rats. Figure 1 shows samples of polygraphic recordings from a newborn rat. During W period a moderate or elevated muscle tonus is present together with eye movements (Fig. 1a). However, during the REM period the tonus of the neck muscle is completely abolished, due to a centrally controlled medullary effect on spinal alpha motoneurons [3], and myoclonic twitches (which are phasic excitations of pontine regions overriding the tonic medullary inhibition), frequent slow and rapid eye movements (either as single movements or as a burst) can be seen (Fig. 1b). These patterns of behavior are generated in the midbrain and in the brainstem. Moreover, this behavior is under control of various brain neurotransmitters: acetylcholine [Ach] is involved in the generation of REM and monoamines (both noradrenaline [NA] and serotonin [5HT] have been demonstrated to regulate the appearance of this behavior [10]. The balance of activity between cholinergic and monoaminergic neurons in the brain determines the behavioral state of the animal [16].

Thus, monitoring behavioral states in infancy is a good indicator of the influence of drugs on brain neurotransmitters and brain physiology. Figure 2 shows an example of the influence of chronic drug treatment, in this case the antidepressant clomipramine, which blocks the uptake of both NA and 5HT, and has some anticholinergic activity, on the ontogeny of REM sleep. After treating baby rats with clonidine, a centrally acting antihypertensive drug which selectively acts on NA neurotransmission in the brain, one also sees a drastic reduction of the amount of time spent in REM sleep, similar to that found with clomipramine (Table 1). The exact neuronal mechanisms underlying eye movements is not yet known, but it has been demonstrated that the dorsolateral part of the pons, the superior colliculi and the cranial occulomotor nucleus are involved in triggering eye movements [27]. Eye movement is one of the components of the behavioral state and the frequency of its appearance can easily be measured. We have also recorded eye movements by direct observation of infant rats, scoring via an event recorder whenever the eye ball is moving. The eye ball is rather large in baby rats and its movements can easily be seen under the sealed eye-lids. A rat pup is put in a small box filled with home nest wood shavings within a recording

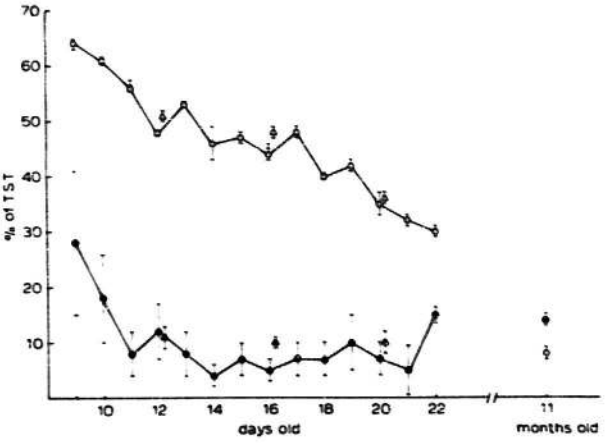

FIG. 2. Maturation of REM (as % of total sleep time: TST) in saline (open circle and triangle) and in clomipramine (filled circle and triangle) treated rats. Each circle represents the mean (SEM) of six 1 hour recordings from 2 animals, whereas each triangle gives the mean (SEM) of fifteen 1 hour recordings from 3 other animals. The adult (11 month) values were calculated from 8 hr continuous recordings in each of 5 animals during the light period; from [18].

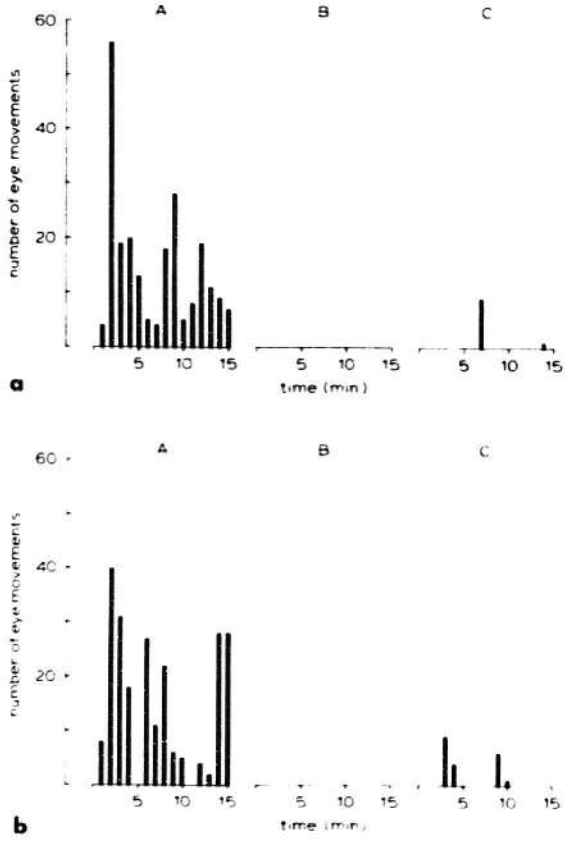

FIG. 3. (a) Number of eye movements during three 15 minutes sleep observations in a 2-day-old rat; A: base line, B: four hours after subcutaneous injection of 15 mg/kg clomipramine, C: eight hours later. (b) Number of eye movements during three 15 minutes sleep observations in two 4-day-old rats; A: a 4-day-old rat subcutaneously injected twice daily with saline from day 2 onwards, B and C are recordings taken from another 4-day-old rat subcutaneously injected twice daily with 100 mg/kg alpha methyl dopa since 2 days of age.

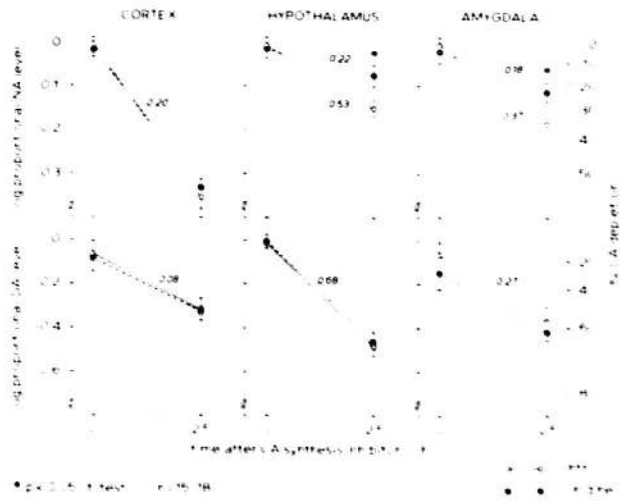

FIG. 4. Catecholamine turnover measured on day 29 in various brain regions after twice daily injections of either saline or clonidine (150 μg/kg/day) from days 8–18 of postnatal life.

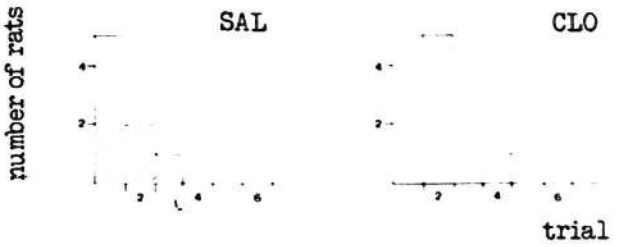

FIG. 5. Trial on which the rats (trained from day 33) first chose the "water" side of the maze.

chamber in which the ambient temperature is kept around 28°C (rat pups do not have auto-thermoregulation until day 8). In such a recording condition animals quickly go to sleep and the number of eye movements can be recorded during the time that the rat is not engaged in gross locomotor activity. These are, therefore, eye movements that take place mainly during sleep. The data can be taped at a low speed, and later frequency histograms can be calculated by computer, running the tape at a high speed (×64). Figure 3a shows the frequency of eye movements during 15 minutes of continuous observation (excluding active waking activity) during baseline conditions and 4 or 8 hr after subcutaneous injection of clomipramine. Figure 3b shows the influence of chronic (from day 2) twice daily subcutaneous injections of either saline or alpha methyl dopa on the frequency of eye movements, in two different 4-day-old rat pups. The drastic reduction of a spontaneously generated brain phenomenon, eye movements, can obviously not be neglected when considering the effect of a drug on the immature nervous system. Furthermore, this measure can easily be obtained in any laboratory without the need of being specialized in sleep physiology.

Studies of behavioral states in the human have been carried out by several investigators [20,28]. It is now established that behavioral states in the human can be observed prenatally from 32 weeks post menstrual gestation period. However, some components of the behavioral states are present much earlier; e.g., eye movements and spontaneous motility (both coordinated and jerky movements) are present from mid gestation in the human fetus [1]. Unfortunately, no attempt has been carried out to study the influence of drugs on, e.g., human fetal eye movements. Some studies recently reported disturbances of the behavioral states of babies from addicted mothers; however, these are in fact effects seen after terminating application of the drug, so that they might be a rebound phenomenon [4]. Recent developments in the ultrasound technique, now routinely used in obstetrics departments for diagnostic purposes, can in the future easily be used to monitor the influence of centrally-acting drugs on fetal behavior states or fetal eye movements.

TABLE 2

SEQUELAE OF CHRONIC DRUG EXPOSURE DURING GESTATION, LABOR, LACTATION AND CHILDHOOD IN MAN AND OTHER MAMMALS*

Drugs	Brain and behavioral alterations in man	Brain and behavioral alterations in animals	REM-sleep deprivation effect	Brain neurotransmitter involved
α-methyl-Dopa	Smaller head circumference, questionable neurological status, increased myoclonic jerks during sleep.	Hyperactivity, delayed motor coordination, hyperanxiety in novel environment.	+++	NA
Propranolol	Smaller head circumference, light for date.	Reduced brain weight and brain/body weight ratios.	+++	NA
Clonidine	Increased myoclonic jerks during sleep, hypotonia, hyperanxiety, minor neurological dysfunction.	Hyperactivity, hyperanxiety, reduced masculine sexual behavior, increased myoclonic jerks during sleep, smaller brain.	+++	NA
Barbiturates	Hyperactivity, restlessness, disturbed sleep, hyperreflexia, reduced responsiveness to sensory stimuli.	Hyperactivity, hyperanxiety, reduced masculine sexual behavior, impairment of learning, reduced responsiveness to sensory stimuli, smaller brain.	++	DA
Reserpine	Anorexia, lethargy.	Smaller brain.	+	NA, DA
Diazepam	Low Apgar, reluctance to eat.	Hyperactivity, learning impairment, reduced acoustic startle reflex.	+	GABA
Imipramine-like compounds	Poor suckling, irritability.	Hyperactivity, hyperanxiety, reduced masculine sexual behavior, increased voluntary alcohol consumption, smaller brain.	+++	5HT, NA, ACh
Chlorpromazine	Extrapyramidal dysfunction: tremor, hypertonus.	Hyperactivity, reduced exploratory behavior, learning impairment, smaller brain.	+	DA
Amphetamine	Withdrawal symptoms.	Marked reduction in ability to habituate to new surroundings. Reduction of dendritic spines and dendritic arborization of cortical neurons.	+	NA, DA

*References in: [31].

Development of Central Neurotransmitters: Influence of Drugs

Another way to demonstrate central influences of medicines, is by measuring brain neurotransmitter activity. Brain neurotransmitters are aminoacids, acetylcholine, amines and peptides. We will concentrate on monoamines, since they have been studied most frequently during development. Furthermore, most of the common psychoactive drugs used in the clinic are known to act on this class of neurotransmitters. Monoamines are among the first neurotransmitters present at early stages of brain development [25]. The NA cells of the locus coeruleus (LC) differentiate on days 10–13 of gestation in the rat, with a peak of heavily labelled cells on day 12, and the 5HT cells of the raphe nuclei and the dopaminergic (DA) cells of the substantia nigra differentiate on days 11–15 (gestational period in the rat is 21 days) [14]. Early appearance of monoaminergic neurons has also been shown in 3–4 month old human fetuses [21]. Pharmacological studies during early development have demonstrated that these amines are functionally mature. High affinity of NA-binding appears on day 18 of gestation in the rat, and NA fibers of newborn rats take up the neurotoxin 6-hydroxy dopamine (6-OH-DA), resulting in a destruction of NA axon terminals. Prenatal treatment with parachlorophenylalanine (PCPA) has been demonstrated to deplete 5HT from rat brain [15]. Using behavioral measures, it was shown that various centrally acting drugs that affect monoamine neurotransmission are functionally active during the neonatal period. Clonidine, a NA agonist, induces hyperactivity during the 1st week of life [12]. Haloperidol, a DA antagonist, induces capaplexy and immobility in both rat and rabbit infants. Furthermore, NA and 5HT reuptake blockers, imipramine and clomipramine influence amine uptake to the same extent as they do in adults [22], and they influence the behavioral states of rats and cats from birth (see above). At the biochemical level the influence of drugs or neurotoxins on monoamines have also been studied. Nomura [23] has shown that depolarizing membranes by increasing the potassium concentration in the medium induced the release of NA, DA and 5HT from brain slices of 2–3 day old

rats to the same extent that it did in brain slices of adult rats. The release of the three amines was markedly inhibited by calcium, although the inhibitory influence of calcium was lower in newborn rat brain slices than in adult. The degree of reuptake of the released amines was of the same order of magnitude in the newborn as in the adult. Nomura concluded that NA, DA and 5HT are already stored in a functionally releasable pool at the nerve terminals of central monoamine neurons in the newborn rat and that these compounds act as neurotransmitters at birth as they do in adulthood [23]. In our own studies, we have shown that chronically treating rats with clonidine during the 2nd and 3rd weeks of life dramatically reduces the amount of time spent in REM sleep [19], and more recently we have demonstrated that such treatment influences NA turnover in the hypothalamus of the young rat (Fig. 4).

It has been shown that both NA and 5HT receptors develop in various brain areas even before the projections from the respective neurotransmitter cell bodies arrive [26,32]. An important role for monoamine receptors during development has been suggested in studies with kittens, in which a good correlation was found between the development of beta adrenergic and 5HT receptors and the critical period for monocular deprivation [9]. Few studies have examined the number of binding sites (B max) and the affinity (Kd) for centrally acting drugs. Nomura [24] has shown that although the number of clonidine binding sites in the cerebral cortex was lower at day 7 than in adults, the Kd values for the high and low affinity binding sites were not significantly different from the adult values after day 7. More studies should be carried out on the long lasting influences of drugs on monoamine receptors. Moreover, since postsynaptic receptors are present before arrival of the neurotransmitter terminals, the modifiability of these receptors as a result of drug treatment is not necessarily similar to the effect on adults. In support of this it has been shown that chronic treatment of infant rats with haloperidol induces hyposensitivity of the DA receptors while similar treatment in adults induces hypersensitivity [30]. In addition, the effect in infancy may be permanent while in adulthood it is transient. Human studies on developmental changes in neurotransmitters as a result of drug therapy are lacking. However, recently studies have been initiated which use human material to study the functional integrity of the monoamine systems.

Developmental Toxicity of Drugs Acting on Brain Neurotransmitters and the Behavioral States

We have studied the influence of two centrally acting drugs, clomipramine and clonidine, both of which influence NA and 5HT neurotransmission and inhibit REM sleep, on behavior in the rat. Rats, neonatally treated with either drug, show hyperactivity, hyperanxiety, reduced sexual behavior and sleep disturbances in adulthood [18,19]. In a more recent study, we have shown that some aspects of associative learning may also be affected by neonatal clonidine exposure. In this study, food deprived animals were trained to enter the left arm of a Y-maze which contained food (while water was available in the right arm). Once rats learned this, they were water-deprived for one day and tested to see when they would enter the right (water) side. Although there was no significant difference between clonidine and control groups during initial training, clonidine treated rats showed a significant delay in choosing the right arm during the testing session (Fig. 5). It has also been shown that neonatal clomipramine treatment increased the adult voluntary alcohol consumption in drug treated rats [7]. Alpha methyl dopa, a false NA transmitter, injected neonatally in kittens, reduced the amount of REM sleep in infancy and produced hyperactivity and hyperanxiety after weaning [29]. The same drug when used in neonatal rats reduced REM sleep and produced hyperactivity and learning difficulties in juvenile rats [11]. Neonatal administration of pargyline and haloperidol, drugs acting on catecholamines, led to sexual dysfunction in adult rats (similar to what we have shown in neonatally clomipramine-and clonidine-treated rats) [6].

Clinical Relevance of Developmental Toxicity Found in Experimental Animals

Table 2 summarizes the influence of several commonly used drugs on brain neurotransmitters and behavioral states. It also shows similarity of a number of effects found in animals and those observed so far in man. However, before one can draw any firm conclusion on extrapolation of all of the animal data to man a number of parameters should be considered. One of these is the dose of drugs used in the animal studies, which in most cases is much higher than the clinical dose. We wish to emphasize the fact that if one takes the dose required to produce similar physiological changes in rat as in man into account, the difference is negligible; e.g., 1 mg/kg clomipramine inhibits REM sleep in man to the same extent that 25 mg/kg does in the rat [18]. This indicates that there are species differences in drug sensitivity and, if physiological effects are indicative of the drug influences, a high dose in the rat can be comparable to a much lower dose in man. We suggest using an animal model that is closer to human from both the physiological condition during the drug therapy (prenatal in man vs. postnatal in rat), as well as adult behavioral complexity. Primate studies are required to fulfill both of these conditions.

Future studies measuring content, turnover and receptor sensitivity of brain neurotransmitters as well as determining physiological responses to drug treatment such as the behavioral states (which are generated exclusively by the brain) in addition to studies on the neurobehavioral consequences of centrally acting drugs in both primates and man will improve our knowledge of developmental toxicity of these drugs.

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