Spontaneous Seizures in Rats Treated with Chlorpromazine During Postnatal Development

Chlorpromazine has been reported to cause convulsions in man and to increase fatality in epileptic patients[1-4]. The present study was designed to investigate the effects of chlorpromazine on maturing rats. Because the neuraxis develops in a characteristic sequence, the developing animal is a suitable model to study and further elucidate convulsant and anticonvulsant properties of drugs on specific CNS structures and several organizational levels[5,6].

Materials and methods. Experiments were performed on Sprague-Dawley rats. Chlorpromazine (CPZ) in doses of either 3 mg, 6 mg, 15 mg or 30 mg/kg body weight was administered s.c. to groups of 2-, 6-, 13-, 20-, or 29-day-old rats. Each dose group consisted of 6 to 8 rats. Controls received the vehicle, water. Chlorpromazine HCl was prepared immediately prior to treatment and was kept in a bottle wrapped with aluminium foil to avoid deterioration as a result of exposure to light[7].

Results and discussion. Upon administration of chlorpromazine to developing rats, spontaneous seizure-like movements such as hyperkinesia, loss of posture, hindlimb clonic-like movements, hyperextension of the head, movements of jaws and forelimb clonus were observed before the onset of tranquilization and sedation. Since the pH of chlorpromazine was 6.3 and that of the water vehicle 7.0, these results cannot be attributed to acidity.

Whereas, all doses of chlorpromazine used produced spontaneous seizurelike phenomena in 6-, 13- and 20-day-old rats, only the high doses of chlorpromazine produced seizure-like activity in 29-day-old rats (Table). These data suggest that perhaps a blood-brain barrier to chlorpromazine may develop in rats after 20 days of age and thus explain the lack of sensitivity to low doses of chlorpromazine in the 29-day-old more mature rats.

The fact that all doses produced seizure-like phenomena in the same percentage of 13-day-old rats cannot be directly explained from these data. However, the second week of postnatal life is characterized as a critical period of brain development during which several enzymes, protein and lipids begin to mature[8]. Therefore, the decrease in the response observed in rats at this age may reflect a temporary decrease in sensitivity.

The spontaneous seizure-like phenomena induced by chlorpromazine appeared to be very similar to the clonic-like movements observed in developing mice before the onset of hypnotic effect of barbital, another CNS depressant[5,6]. However, barbital-induced clonic-like movements are not consistently exhibited by mice before 18 days of age, whereas chlorpromazine-induced seizure-like

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Chlorpromazine-induced seizure-like activity in developing animals

Treatment[a]	Animals exhibiting seizure ativity (%)	Type of seizure activity
CPZ-2 day		
3 mg/kg	0.0	Hyperkinesia, loss of posture (rolling over on back), hindlimb clonic-like movements
6 mg/kg	37.5	
15 mg/kg	75.0	
30 mg/kg	75.0	
CPZ-6 day		
6 mg/kg	57.0	Loss of posture (rolling over on back), hindlimb clonic-like movements, vocalizing
15 mg/kg	50.0	
30 mg/kg	87.5	
CPZ-13 day		
6 mg/kg	25.0	Movements of jaws (chewing-like), loss of posture (rolling over on back), hindlimb clonic-like movements, hyperextension of the head
15 mg/kg	37.5	
30 mg/kg	37.5	
CPZ-20 day		
3 mg/kg	25.0	Movements of jaws (chewing-like), teeth grinding, vocalizing
6 mg/kg	50.0	
15 mg/kg	87.5	
30 mg/kg	75.0	
CPZ-29 day		
3 mg/kg	0.0	Movements of jaws (chewing like), head shaking, forelimb clonus
6 mg/kg	0.0	
15 mg/kg	37.5	
30 mg/kg	37.5	

[a] Chlorpromazine HCl was administered s.c. to female rats of either 2, 6, 13, 20 or 29 days of age (CPZ-2, CPZ-6, CPZ-13, CPZ-20 and CPZ-29). Each age group was subdivided into 3 or 4 subgroups, each receiving a dose of either 3 mg/kg, 6 mg/kg, 15 mg/kg or 30 mg/kg body weight of chlorpromazine.

phenomena were present as early as 2 days of age (Table). The barbital-induced pre-sleep clonic-like movements have been interpreted to be a result of depression of inhibitory systems by barbital, the so-called 'release phenomenon'. It can further be speculated that the seizure-like movements induced by chlorpromazine may be a result of depression of some subcortical and spinal cord inhibitory systems which are ordinarily functioning as early as 2 days of age in rats. Recent pharmacologic studies have shown that rats are responsive to the arousal effects of amphetamine as early as 10 days after birth; amphetamine mimics adrenergic transmission by release of norepinephrine[9]. Both norepinephrine and dopamine, putative neurotransmitters, have been implicated in the CNS effects of chlorpromazine[10]. That chlorpromazine may depress some inhibitory systems and thus produce excitation is supported by the view that the chlorpromazine-induced Parkinsonism may be a result of depression by chlorpromazine of inhibitory dopaminergic neurons in the basal ganglia[10,11].

Zusammenfassung. Nachweis eines epileptogenen Effektes sowie Beurteilung von Dosis- und Altersabhängigkeit von Chlorpromazin (Largactil) bei neugeborenen und jungen Ratten.

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Increased Proliferation of Rat Mesothelial Cells after Intraperitoneal Endotoxin Injection

Endothelial cells of the blood vessels are sensitive to parenteral injection of endotoxin: 72 h after the i.v. injection of the polysaccharide, increase of endothelial cell proliferation is initiated (GAYNOR[1]). Mesothelial cells are more easily obtained than endothelial cells and are in some instances comparable with endothelial cells (COTRAN und MAJNO[2]). We observed the effect of different doses of endotoxin on mitotic activity of mesothelial cells in rats after intraperitoneal injection.

25 SIV-50 rats (S. Ivanovas, Kisslegg/Allgäu, 4 weeks old, 70 g body wt.) were used in these experiments. As shown in the Table, experimental animals were injected with different doses of endotoxin (*Salmonella marcescens*, Difco Laboratories, Detroit); 48 h after the endotoxin injection animals were sacrificed. 'Häutchen'-preparations of the parietal mesothelium (abdominal wall and diaphragma) were prepared according to the method of BENEKE et al.[3] after silver impregnation of cell boarders with $AgNO_3$. The preparations were stained with hematoxylin-eosin and the mitotic rate was determined.

In 4-week-old control animals, mitosis of mesothelial cells are rarely seen (Figure 1). There are about 0.2% mesothelial cells with caryokinetic figures; 48 h after the i.p. injection of endotoxin, there is an increase of mitotic activity (Figure 2) in mesothelial cells. This increase is independent of the doses of endotoxin used (Figure 1). An increased number of caryokinetic figures could be observed in about 60% of the animals. In the remaining 40%, mitotic indices were comparable with that of control animals. In animals with a higher rate of proliferating cells, morphological changes of mesothelial cells were observed: silver stained cell boarders, which are narrow in control animals, were often broadend or absent in some experimental animals. Furthermore, in some animals signet ring cells (previously described after i.p. PHA-injection, MOHR et al.[4-7]) appeared in the mesothelial cell layer (Figure 3). Signet ring cells were preferentially found in mesothelial cell preparations of the diaphragma.

The increased proliferation of mesothelial cells after i.p. injection of endotoxin is comparable to the reaction of

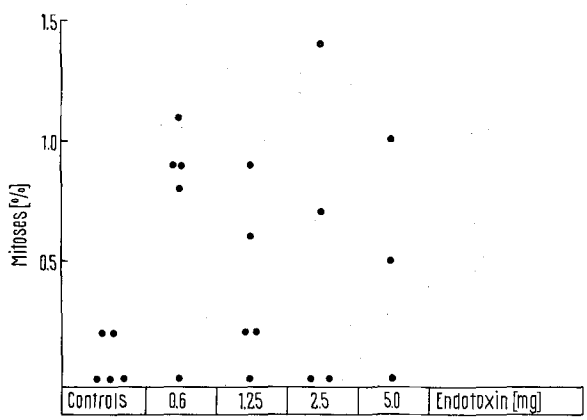

Fig. 1. Mitotic rate of parietal mesothelial cells in control animals and experimental animals 48 h after i.p. injection of different doses of endotoxin.

Experimental design

		Endotoxin (mg)			
		0.6	1.2	2.5	5.0
Control animals	5				
Injected animals		5	5	5	5
Surviving animals		5	5	4	3

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