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Drug interaction—Effect of chlorpromazine on the disposition of 8-^{14}C-mescaline in fetal and maternal brain and liver in pregnant mouse

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Recent studies by us on the placental transfer of mescaline in pregnant mice have shown that the hallucinogen crossed the placenta and accumulated in readily measurable amounts in the whole fetuses and fetal tissues.[1] Wurtman and Axelrod[2] have shown that pretreatment of rats with chlorpromazine, 20 mg/kg, caused marked accumulation of ^{3}H-melatonin by all the organs studied. More recently, Lemberger *et al.*[3] reported marked elevation of ^{3}H-amphetamine in the brain of rats pretreated with 15 mg/kg of chlorpromazine. Observations from our laboratory have shown that pretreatment of adult male mice with chlorpromazine, 15 mg/kg, 30 min prior to or 45 min after administration of ^{14}C-mescaline resulted in marked prolongation of the disappearance of mescaline from the brain and several other tissues.[4] Interestingly, chlorpromazine and other phenothiazines have been employed to treat the toxicity induced by amphetamine, lysergic acid diethylamide (LSD), mescaline and other hallucinogens.[5–7] The aim of this study is to report the effects of different doses

TABLE 1. EFFECT OF PRETREATMENT OF CHLORPROMAZINE ON THE LEVELS OF UNCHANGED ^{14}C-MESCALINE IN MATERNAL AND FETAL BRAIN AND LIVER*

Treatment	Radioactivity (dis/min/g wet wt tissue (4 hr after mescaline)					
	Maternal brain	Fetal brain	Difference (%)	Maternal liver	Fetal liver	Difference (%)
Saline	933 ± 160 (4)	2,869 ± 652 (12)	308	3,906 ± 966 (4)	3,362 ± 585 (12)	86
Chlorpromazine	4,175 ± 592 (3)	15,525 ± 708 (9)	372	19,651 ± 1,189 (3)	18,416 ± 2,720 (9)	94
Difference (%)	447	541		503	548	
P value	< 0·001	< 0·001		< 0·001	< 0·001	

* Chlorpromazine (15 mg/kg) was injected i.p. 30 min prior to administration of 2 μCi ^{14}C-mescaline to pregnant mice on days 15–18 of gestation. The animals were sacrificed 4 hr after mescaline. The values are averages of three to four separate experiments ± standard deviation of the mean. The statistical significance of differences between mean values was determined with a two-tailed Student's *t*-test.

of chlorpromazine treatment to pregnant mice on the disposition of injected labeled mescaline in maternal and fetal brain and liver.

The 8-^{14}C-mescaline hydrochloride (sp. act., 4·53 mCi/m-mole) was purchased from New England Nuclear Corp. Chlorpromazine hydrochloride was received as a gift from Smith, Kline & French Laboratories.

One female and one male mouse of albino Swiss–Webster strain were left together for mating in a separate stainless steel cage from 4:00 p.m. to 8:30 a.m. The copulation was ascertained by the presence of a vaginal plug. When the plug was seen, the female was removed and housed separately. This time was designated day 1 of pregnancy. Pregnant mice on approximately days 15–18 of gestation were injected i.p. with chlorpromazine hydrochloride (5·0, 7·5 or 15·0 mg/kg) in 0·5 ml saline; control animals were given the same volume of saline. Thirty min later, the animals were given 8-^{14}C-mescaline hydrochloride (36 μCi/kg; 8·33 μmoles/kg). A group of three mice received mescaline first, and 45 min later were given chlorpromazine (5·0 mg/kg). The environmental temperature was 23 $\pm$ 0·5°; in some experiments the animals were kept in a room thermo-regulated at 30 $\pm$ 0·5° to avoid hypothermia caused by chlorpromazine.[8] In addition, body temperature was maintained by allowing chlorpromazine-treated mouse to huddle in a small closed cage with four normally active animals as reported by Schanberg *et al.*[9] Mice were sacrificed by neck fracture 4 hr after mescaline. The whole fetuses, maternal brain and liver were frozen on dry ice and kept in deep freeze at −20° for 24 hr. The radioactivity in fetal and maternal brain and liver was extracted in chilled 0·4 N perchloric acid. The details are given elsewhere.[10] Unchanged mescaline was isolated from its metabolites according to the procedure outlined by Charalampous *et al.*,[11] with slight modifications.[12] The neutralized perchloric acid extracts were allowed to pass on columns 50 mm long with an internal diameter of 4·2 to 4·5 mm and containing Dowex 50 W-X$_4$, 200–400 mesh, previously buffered at pH 5·8 with phosphate buffer. The overall recovery through the isolation procedure ranged from 75 to 82 per cent; the values reported are corrected for the recovery. Aliquots of 1·0 ml of extracts were added to 10 ml of scintillation fluid and the radioactivity was assayed in a Nuclear Chicago Mark II liquid scintillation system using ^{133}Ba as an external standard. The counting efficiency ranged from 87 to 91 per cent. The counts were converted to 100 per cent efficiency and reported as dis./min/g of wet weight tissues.

A dose of 15·0 mg/kg of chlorpromazine was chosen on the basis of similarity to clinical dose and lack of toxicity documented by Mahju and Maickel,[13] who employed chlorpromazine ,18·0 mg/kg, in their studies. Within 10 min after chlorpromazine (15 mg/kg), animals were tranquilized, as evidenced by the loss of locomotor activity. The effect lasted for the entire period of observation. Table 1 reports the levels of mescaline in the brain and liver of fetuses and mother at 4 hr after mescaline. The per cent differences in the levels of mescaline in maternal and fetal tissues are shown on the top horizontal line. In the saline-treated group, the levels of mescaline in the fetal brain were 308 per cent of that of maternal brain. Such a striking difference was unnoticeable in the liver in which the level in the fetal tissue was 86 per cent of that of mother. The per cent differences in the levels of mescaline in saline-treated and chlorpromazine (15·0 mg/kg)-pretreated mice are shown on the vertical lines. Pretreatment with chlorpromazine resulted in marked accumulation of mescaline in both maternal and fetal brain as well as liver; the levels of mescaline were almost four to five times more in the chlorpromazine-pretreated group as compared to those in corresponding tissues in the saline-treated group. In chlorpromazine-pretreated animals, the levels of mescaline in fetal brain and liver were 372 and 94 per cent, respectively, of that of maternal tissues. These differences in the maternal and fetal tissue levels are somewhat higher in chlorpromazine-pretreated animals as compared to saline-pretreated controls.

The levels of mescaline, as dis/min/g, in tissues of mice injected with chlorpromazine, 5·0 mg/kg, 30 min prior to and sacrificed 4 hr after the hallucinogen were: brain, 2996 $\pm$ 220 (mother), 10,655 $\pm$ 1689 (fetus); and liver, 14,665 $\pm$ 3354 (mother), 12,038 $\pm$ 1911 (fetus). Mice pretreated with 7·5 mg/kg had tissue levels of mescaline identical to those measured with a 5·0 mg/kg dosage. A group of three pregnant mice received mescaline; chlorpromazine, 5·0 mg/kg, was given 45 min after mescaline and the animals were sacrificed 4 hr after the administration of hallucinogen. The mescaline contents were: brain, 3605 $\pm$ 338 (mother), 13,031 $\pm$ 2360 (fetus); and liver, 11,229 $\pm$ 2832 (mother), 10,985 $\pm$ 3109 dis/min/g. In the course of our experiments, at an environmental temperature of 30 $\pm$ 0·5°, roughly the same effects were induced by different doses of chlorpromazine as at normal room temperature, 23 $\pm$ 0·5°. Thus, groups of mice left at a temperature regulated at 30 $\pm$ 0·5° had tissue levels of mescaline identical to those in mice kept at room temperature of 23 $\pm$ 0·5°.

In the present investigation, the levels of unchanged ^{14}C-mescaline were measured in the fetal and maternal brain and liver 4 hr after i.p. administration of labeled mescaline to the mother. In the control animals, the fetal brain had accumulated three times more mescaline than the maternal brain. Even at the 15-min time period, the level of mescaline in the fetal brain was more than twice that of maternal brain.[1] The rapid accumulation of mescaline in high concentrations and its subsequent slow disappearance may result from a partially developed blood–brain barrier and a less efficient mechanism for disposition of the drug. An analysis of the concentration of mescaline in the brain and liver

revealed that both low and high doses of chlorpromazine caused a marked and prolonged retention of mescaline, and that this effect was unrelated to the chlorpromazine-induced hypothermic response. Chlorpromazine perhaps interferes with the processes that remove mescaline from the tissues. Thus, chlorpromazine would have an effect on the elimination of mescaline by blockade of efflux processes, by increased binding to subcellular particles, or by diminished neural activity. Phenothiazines are known to influence the membrane transport mechanism.[14] Previous studies on subcellular distribution revealed that from two-thirds to three-fourths of mescaline in the liver and brain remained in the soluble supernatant fraction after i.p. administration of mescaline to mice.[15]

In a clinical situation, the manifestations of mescaline toxicity or psychosis are already present before an antipsychotic agent is administered. In our studies, chlorpromazine (5·0 mg/kg) was injected 45 min after mescaline to observe the effects on the previously administered hallucinogen. Under the experimental condition, chlorpromazine markedly blocked the disappearance of mescaline from the fetal and maternal brain and liver. These findings may have a potential significance in view of the interaction between an antipsychotic agent and a hallucinogen. Recently, disturbing effects of chlorpromazine on adverse LSD and amphetamine reactions have been reported in humans.[16]

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3,4-Benzpyrene and aniline are hydroxylated by human fetal liver but not by placenta at 6–7 weeks of fetal age

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IN RECENT years the ability of the human fetal liver to metabolize drugs and other foreign compounds has been demonstrated by many authors.[1–12] Juchau[11] has shown that the nitro group can reduce *p*-nitrobenzoic acid as early as the seventh week of fetal age. Pelkonen[13] has shown that several oxida-