Chemical (HCB) Porphyria: Effect of Removal of Sex Organs in the Rat

by D. L. GRANT, J. B. SHIELDS, and D. C. VILLENEUVE

Health Protection Branch
Bureau of Chemical Safety
Health & Welfare Canada
Ottawa, Ontario, Canada
K1A 0L2

Hexachlorobenzene (HCB) has been shown to cause porphyria in a number of animals species (STRIK 1973). The rat has been used as a model for studying porphyria cutanea tarda. Female rats have been shown to be more sensitive to acquiring chemical (HCB) porphyria than male rats (GRANT et al. 1974). IPPEN and AUST (1972) reported that a dietary level of 2000 ppm HCB increased the urinary excretion of porphyrins and that the simultaneous administration of estradiol or estradiol with gestagen and androgen greatly enhanced the quantity of porphyrins excreted. Estrogens have induced porphyria cutanea tarda in humans (ZIMMERMAN et al. 1966 & VAIL 1967). A study on the effect of removal of the testes and ovaries on the accumulation of porphyrins in the liver of rats fed graded levels of HCB was carried out.

Methods and Procedures

Diet

HCB, organic analytical standard grade (BDH Chemicals Ltd., England), was mixed with a standard ground commercial diet (Maple Leaf Mills, Master Feeds Division, Toronto) plus 3% corn oil to give dietary levels of 100 and 500 ppm. When fed ad libitum these concentrations were considered to be equivalent to 5 and 25 mg/kg.

One hundred Sprague-Dawley weanling rats were randomly divided into 4 groups (2 X 25 males and 2 X 25 females). One group of males and one group of females had their testes or ovaries removed under ether anaesthesia. The rats were kept in an environmentally controlled room at 22°C with the lights on from 0700 to 1900 hr. At 32 days of age each group was divided into 2 subgroups and fed the 100 or 500 ppm diet. Five rats were killed from each subgroup at specified times and livers removed, weighed and homogenized with 9 volumes of distilled water. Aliquots of the homogenate were analyzed for porphyrins (ABBRITTI and DE MATTEIS, 1972 and GRANT et al. 1974).

Bulletin of Environmental Contamination & Toxicology,
Vol. 14, No. 4 © 1975 by Springer-Verlag New York Inc.

Results & Discussion

Female rats had higher levels of hepatic porphyrins than male rats (Table 1). This agrees with previous findings (GRANT et al. 1974a, 1974b). This great difference due to sex in the induction of porphyria by HCB is not apparent in mice as male and female mice fed a diet containing 175 ppm HCB for 134 days had liver porphyrin levels (nM/g) of 14.2 and 2.2 respectively (GRANT 1975). The removal of the testes increased the quantity of porphyrins in the liver of rats fed 100 ppm HCB (Table 1). In the case of females, removal of the ovaries decreased the level of porphyrins accumulated in the liver. However, dietary level of 500 ppm HCB appeared to mask the effect of removal of sex organs on the accumulation of porphyrins in the liver. HCB acquired porphyria develops slowly in the rat. No value for normal females fed 500 ppm HCB for 73 days is presented because 4 of the 5 animals died.

The mechanism by which HCB affects porphyrin synthesis in the rat has not yet been defined. GAJDOS and GAJDOS-TOROK (1961) have shown that adenosine-5-monophosphoric acid (AMP) has a therapeutic effect (decreased excretion of uroporphyrins and disappearance of neurological symptoms) on HCB induced porphyria. JOUBERT et al. (1973) have suggested that the accumulation of iron in the liver limits the decarboxylation of uroporphyrinogen. The results presented here and the work of IPPEN and AUST (1972) show that the steroids produced by the ovaries and testes are involved in the mechanism by which HCB induces porphyria in the rat.

The induction of porphyria by HCB depends on species, sex, age, dosage level and length of exposure. All these factors are important and should be considered when studying the induction of porphyria by HCB.

Acknowledgements

The authors wish to acknowledge the help of the Animal Resources Division for preparation and care of rats.

TABLE 1

Liver porphyrin[a] levels in rats fed HCB

HCB (ppm)	100			500	
Group	Days on Test				
	73	129	183	43	73
Male[b]	0.2[e] ± 0.1[f]	0.5 ± 0.1	1.1 ± 0.3	0.8 ± 0.2	8 ± 4
Male[c]	0.4 ± 0.2	21 ± 11	14 ± 8.1	1.7 ± 0.7	3 ± 1
Female[b]	121 ± 106	306 ± 109	413 ± 70	33 ± 11	-
Female[d]	13 ± 10	68 ± 37	28 ± 6	25 ± 13	9 ± 3

a nM/g liver, calculated as coproporphyrin.

b Normal.

c Castrated.

d Ovariectomized.

e Mean of 5 determinations.

f Standard error of mean.

References

ABBRITTI, G., & F. DE MATTEIS:
Chem. Biol. Interactions 4, 281 (1971/1972)

GAJDOS, A. & M. GAJDOS-TOROK:
The Lancet ii, 175 (1961)

GRANT, D.L., F. IVERSON, G.V. HATINA & D.C. VILLENEUVE:
Environ. Physiol. 4, 159 (1974a)

GRANT, D.L., G.V. HATINA & I.C. MUNRO:
I.U.P.A.C. Meeting Paper 269, Helsinki (1974b)

GRANT, D.L.
(1975 Unpublished)

IPPEN, H. & D. AUST
Klin. Wschr. 50, 793 (1972)

JOUBERT, S.M., J.J.F. TALJAARD & B.C. SHANLEY:
Enzyme 16, 305 (1973)

STRIK, J.J.T.W.A.:
Enzyme 16, 224 (1973)

VAIL, J.T.:
Jama 201, 671 (1967)

ZIMMERMAN, T.S., J.M. McMILLIN & C.J. WATSON:
Arch. Intern. Med. 118, 229 (1966)