Effects of Inositol, Diphenylhydantoin and Phenobarbital on HEOD Storage in Rat Adipose Tissue*

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It has been shown by DAVIES et al(1969)that diphenylhydantoin and phenobarbital decrease the body burden of DDT in humans and diphenylhydantoin decreases the body burden of DDT in rats Phenobarbital decreases the body burden of HEOD in rats but a similar effect for diphenylhydantoin has not been demonstrated. Inositol is used in poultry rations to prevent fatty livers in laying hens. Since inositol may in some way affect fat metabolism, it has been proposed that this water soluble vitamin might decrease the body burden of chlorinated hydrocarbon pesticides.

The object of this investigation was to compare the effects of diphenylhydantoin and inositol with those of phenobarbital on HEOD (the major component of dieldrin) storage in rat adipose tissue.

Methods

Experiment 1. Eighty-eight male rats were divided into 22 groups of 4 rats each. Both the HEOD contamination and decontamination period were for two weeks. HEOD was mixed in the feed at the level of 10 PPM. The rats were fed ad lib. In all experiments phenobarbital, diphenylhydantoin and inositol were mixed in the feed at the levels of 500, 500 and 1000 PPM respectively. Four groups of rats served as controls. The drugs and vitamin were fed throughout the entire 4 weeks and only during the last 2 weeks.

Experiment 2. Diphenylhydantoin, inositol, and diphenylhydantoin plus inositol were fed for 4 weeks after the 2 week HEOD contamination period. There were four rats per group. HEOD concentration in adipose tissue, body weight and enzyme activity was determined for each rat. The data plotted represent the average for each group.

HEOD concentrations in adipose tissue were determined by methods previously described. (COOK, R. M. 1970, WILSON, K. A., and R. M. COOK. 1972).

Aminopyrine demethylase activity in liver microsomes was determined as previously described. (COOK, R. M., and K. A. WILSON, 1970).

*Supported in part by EPA Grant No. R800770 and the Michigan Agricultural Experiment Station (Journal Article No. 5950).

Bulletin of Environmental Contamination & Toxicology,
Vol. 9, No. 6, © 1973 by Springer-Verlag New York Inc.

Results and Discussion

The effects of the treatments on body weight gains are shown in figure 1. During the first two weeks the gains were similar for all treatments. When HEOD feeding ceased, increase in weight gain was slight for the control rats. However, phenobarbital and diphenylhydantoin both appeared to stimulate weight gain after HEOD feeding ceased. Body weights for the group fed inositol were only slightly higher than the controls.

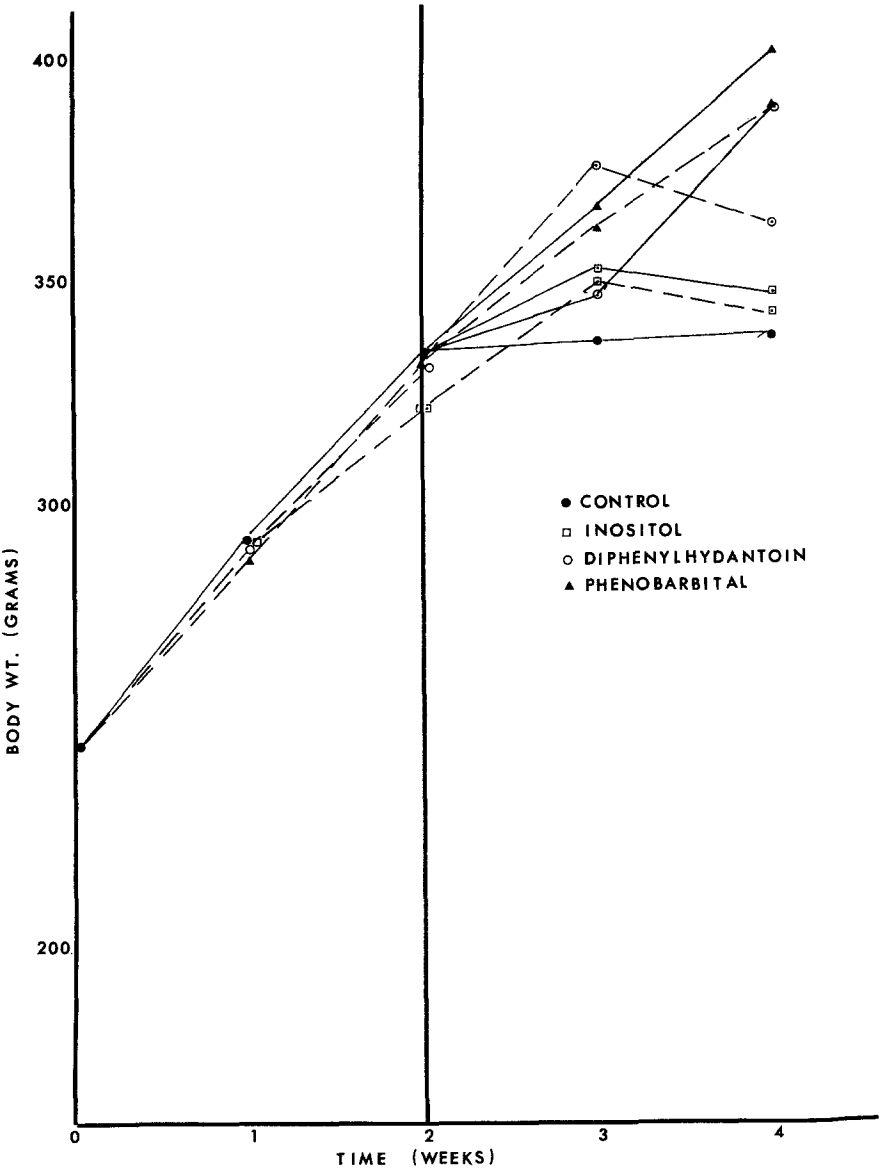

FIGURE 1. Effects of phenobarbital, diphenylhydantoin and inositol on the body weight of rats.

Aminopyrine demethylase activity in liver microsomes is presented in figure 2. Phenobarbital markedly increased enzyme activity. Diphenylhydantoin and inositol were not major inducers of aminopyrine demethylase.

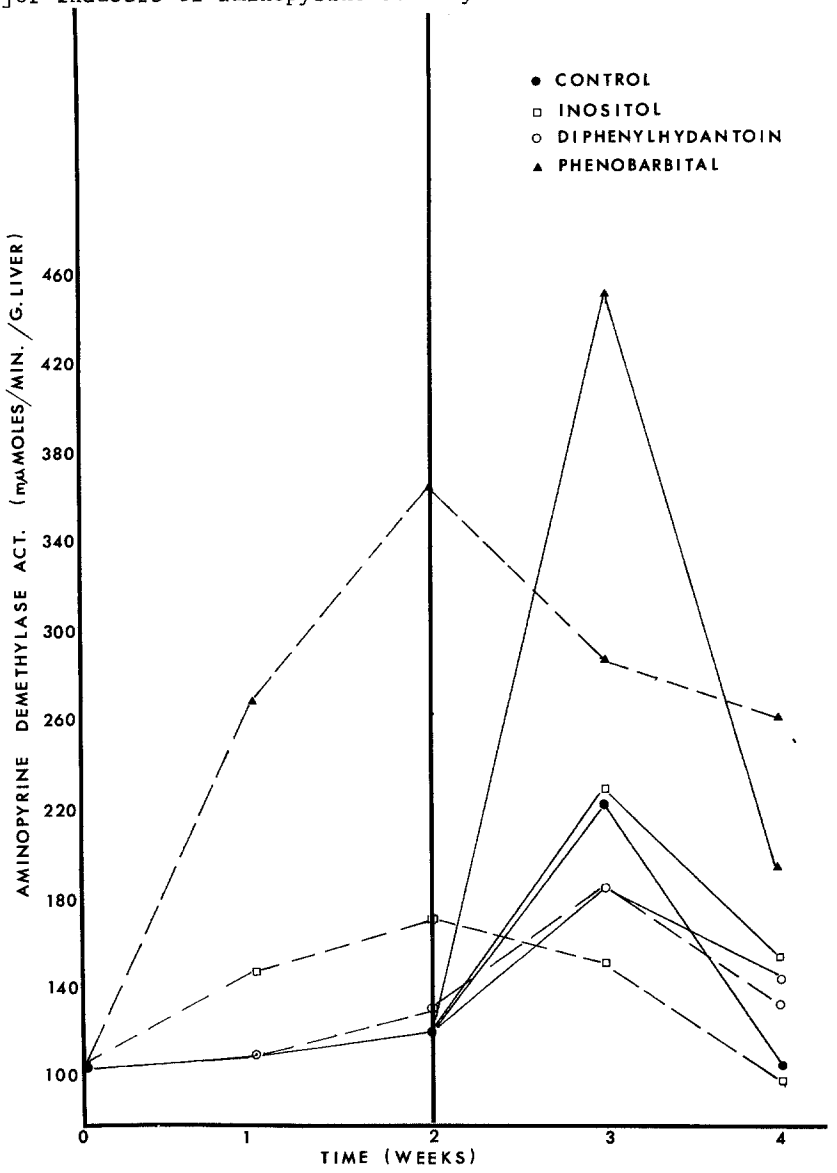

FIGURE 2. Effects of phenobarbital, diphenylhydantoin, inositol and HECD on aminopyrine demethylase activity in rat liver microsomes.

The data in figure 3 show that in contrast with phenobarbital, diphenylhydantoin and inositol when fed for 2 weeks after HEOD feeding ceased did not decrease the concentration of HEOD in adipose tissue. However, when fed simultaneously with HEOD both phenobarbital and diphenylhydantoin prevented the normal appearance of HEOD in body fat. Phenobarbital was more effective than diphenylhydantoin.

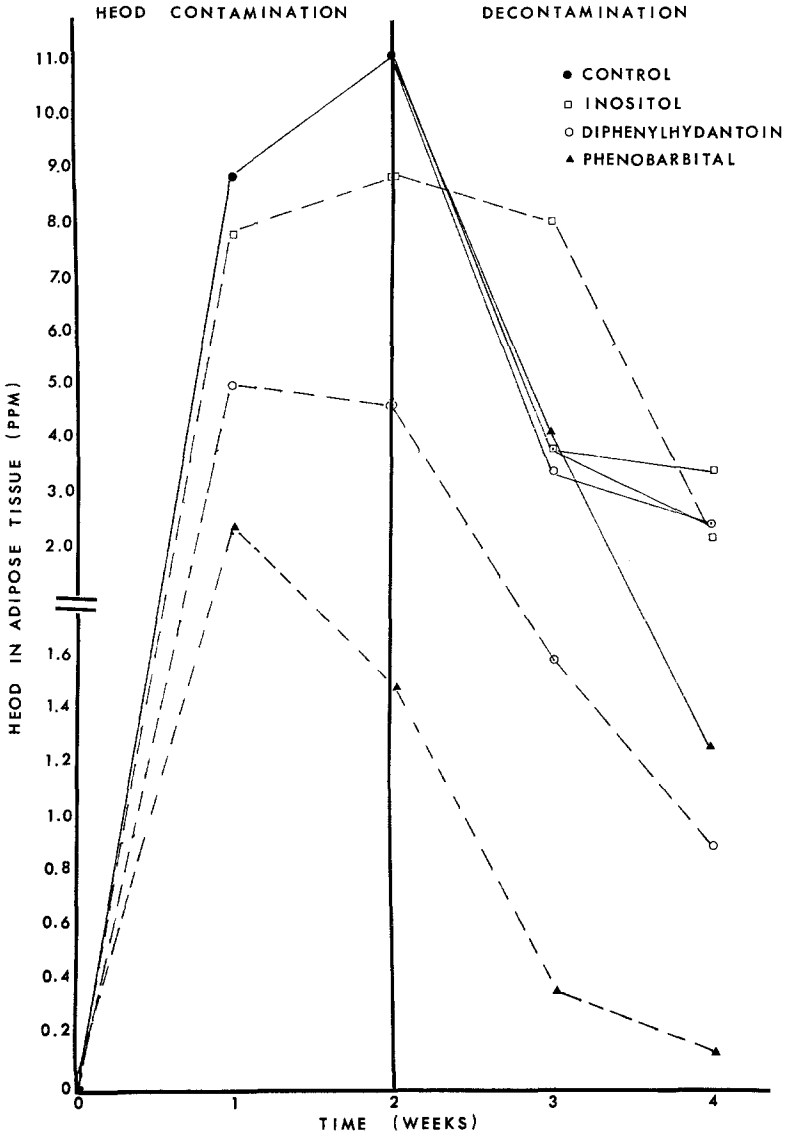

FIGURE 3. Effects of phenobarbital, diphenylhydantoin and inositol on HEOD levels in adipose tissue.

Since diphenylhydantoin and inositol when fed for 2 weeks did not decrease HEOD levels in body fat below control values, a second experiment was conducted in which the decontamination time was for 4 weeks instead of 2 weeks. The data in figure 4 show that both diphenylhydantoin and inositol decrease HEOD levels in adipose tissue when fed 4 weeks but not when fed for only 2 weeks. Thus, these chemicals must be fed for a longer period than phenobarbital in order to observe an effect on HEOD levels in adipose tissue. The combination of diphenylhydantoin plus inositol was not as effective as either chemical alone.

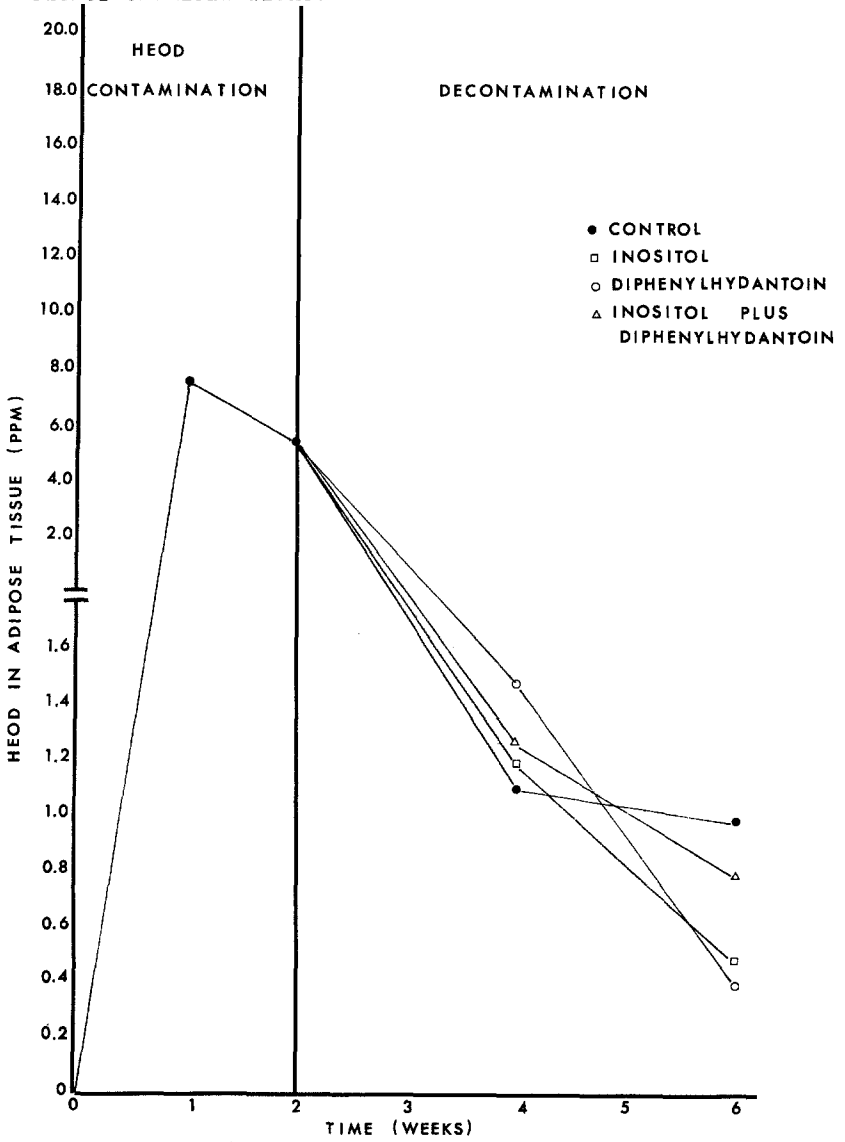

FIGURE 4. Effect of diphenylhydantoin, inositol and diphenylhydantoin plus inositol on HEOD levels in rat adipose tissue.

These experiments raise interesting questions about the mechanism of action of inositol. Presumably this vitamin does not induce drug-metabolizing enzymes in liver microsomes that would metabolize HEOD at a faster rate. However, it is possible that inositol provides a source of glucuronic acid which may stimulate the synthesis of a glucuronide from a HEOD metabolite. Inositol did not appear to decrease adipose tissue levels since weight gains were similar to those of control animals (figure 3).

Diphenylhydantoin is believed to induce drug-metabolizing enzymes in liver microsomes and in this way to increase the metabolism and excretion of DDT. The drug does not markedly affect the activity of aminopyrine demethylase even when fed for 4 weeks. However, it is well known that certain drugs induce the activity of only one or two enzymes whereas other drugs such as phenobarbital induced the activity of many different enzyme-catalyzed reactions in liver microsomes. Diphenylhydantoin most likely induces the activity of HEOD metabolizing enzymes in liver microsomes.

The effects of phenobarbital and diphenylhydantoin on body weight gains may be due to a tranquilizing effect of both drugs.

In summary, these experiments show that phenobarbital, diphenylhydantoin and inositol at the levels fed decreased the concentration of HEOD in rat adipose. However, diphenylhydantoin and inositol had to be fed 2 weeks longer than did phenobarbital to observe this effect.

Acknowledgment

The technical assistance of Mrs. Lea Stomoudis is gratefully acknowledged.

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