tent being markedly affected. Under the present experimental conditions the likelihood of such events is remote but the observation in the present investigation that changes in blood histamine concentration can make a significant contribution to estimates of brain histamine content, illustrates the need for caution in the interpretation of experimental findings.

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## Absence of increased carnitine acetyltransferase activity in the liver with proliferation of smooth endoplasmic reticulum

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Carnitine acetyltransferase (CAT; EC 2.3.1.7) of rat liver has been shown by Markwell *et al.* [1, 2] to be distributed among the mitochondrial, peroxisomal and microsomal fractions. Previous work from our laboratory has demonstrated that the marked increase in CAT activity in the livers of rats and mice treated with several hypolipidemic drugs is, to a large extent, due to the striking increase in peroxisome population [3–5]. As the subcellular distribution of CAT is heterogenous in nature, and since the drugs that induce peroxisome proliferation also cause a concomitant increase in smooth endoplasmic reticulum (SER) [5–7], the possibility that SER may also contribute to the CAT increase could not be ruled out. The present study was undertaken to ascertain if compounds capable of inducing proliferation of SER can cause an increase in CAT activity in the liver.

Male F-344 rats (Simonson Labs, Inc., Gilroy, CA) were treated for 1 week with a peroxisome proliferating agent, clofibrate (ethyl-α-*p*-chlorophenoxyisobutyrate) [6, 8], or with drugs known to induce the proliferation of hepatic SER [9–11]. These are: phenobarbital (Winthrop Labs, New York, NY), allylisopropylacetamide (AIA; Hoffmann-LaRoche, Inc., Nutley, NJ) and [1-(*o*-chloraphenyl)-1-(*p*-chlorophenyl), 2,2-dichloroethanc] (*o,p*-DDD; Aldrich

Table 1. Effect of compounds that induce proliferation of hepatic peroxisomes or smooth endoplasmic reticulum on liver weight and carnitine acetyltransferase activity in male F-344 rats

| Treatment* | No. of animals | Liver wt (g/100 g body wt) | Hepatic CAT activity (units/mg protein) |
|---|---|---|---|
| Control diet | 4 | 4.52 ± 0.06† | 3.3 ± 0.4 |
| Clofibrate (100 mg/kg; gavage 2 times daily) | 4 | 6.13 ± 0.38‡ | 57.8 ± 6.2‡ |
| Phenobarbital (100 mg/kg; i.p. once daily) | 5 | 4.98 ± 0.04‡ | 1.2 ± 0.3§ |
| Allylisopropylacetamide (200 mg/kg; S.C.; 2 times daily) | 5 | 6.07 ± 0.24‡ | 4.2 ± 1.4 |
| o,p-DDD (200 mg/kg; i.p. once daily) | 5 | 4.15 ± 0.10§ | 3.2 ± 0.9 |

* All animals were treated for 7 consecutive days. Most received a single dose, except for clofibrate and AIA groups which received 2 doses/day.
† Values are expressed as mean ± S. E.
‡ Significantly different from control, $P < 0.001$.
§ Significantly different from control, $P < 0.05$.

Chemical Co., Inc., Milwaukee, WI). The dose and route of administration of each compound is presented in Table 1.

The effectiveness of organelle proliferation in these experiments was monitored by the examination of thin sections of liver tissue, under the electron microscope. In animals treated with clofibrate, a marked increase in the number of peroxisomes as well as a moderate increase in SER was noted in the liver cells. In animals treated with phenobarbital, AIA or *o,p*-DDD only a marked increase in SER was observed. The increase in liver weight was more pronounced in animals treated with clofibrate and AIA (Table 1). The changes noted in hepatocyte ultrastructure and liver size with these compounds were consistent with previous reports [6, 10].

The CAT activity was measured on supernatants (105,000 *g* for 60 min) of sonified rat liver homogenates, as previously described [3], using the thio-acceptor, [5,5'-dithio-bis-(2-nitrobenzoate)] (DTNB). The release of CoA from acetyl CoA in the presence of carnitine was measured at 412 nm. The hepatic activity of CAT was increased only in rats treated with the peroxisome proliferator, clofibrate (Table 1). None of the agents which induced a significant proliferation of SER were effective in increasing the activity of hepatic CAT. In fact, a small but significant decrease in hepatic CAT activity was observed in animals treated with phenobarbital. It appears, therefore, that the increased hepatic CAT activity is specific only for drugs which elicit peroxisome proliferation.

As all agents that induce hepatic peroxisome proliferation also have been found to have a hypolipidemic effect [7, 12], the the associated increase in hepatic CAT activity may be related to their hypolipidemic property. Lazarow and de Duve [13] have recently found $\beta$-oxidative activity of palmitoyl CoA in peroxisome fractions from rat liver and showed that this activity increased markedly in rats treated with clofibrate. These studies, therefore, appear to support our contention that the drug-induced peroxisome proliferation is related to lipid metabolism [7].

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