Octanoate oxidation in the cerium-induced fatty liver

Cerium and certain other rare earths, when administered intravenously to rats, produce a fatty liver[1,2]. The purpose of the experiments reported here was to determine the relationship, if any, between fatty acid oxidation and the lipid and the cerium content of the liver after the administration of rare-earth metal.

Female Carworth-Farms-Nelson strain rats weighing between 150 and 200 g were maintained on a Dietrich and Gambrill rat laboratory chow. Fatty livers were produced by administering cerium (2 mg/kg) as the chloride by a tail-vein injection[1,2]. The rats were killed at various times after the rare-earth injection. All animals were fasted 24 h before sacrifice. The oxidation of octanoic acid by rat-liver mitochondria[3] was measured using the procedure described by LEHNINGER[4]. Redistilled octanoic acid was prepared as the potassium salt for use in all Warburg experiments. The results for the octanoate oxidation were expressed as μmoles O_2/mgN/h. A semi-micro-Kjeldahl method[5] was used for analysis of the tissue nitrogen. In another group of rats the amount of cerium remaining in the liver after the injection was determined from the distribution of tracer ^{144}Ce(25–30 μC) that had been incorporated into the 2 mg/kg cerium dose. The livers were wet ashed with boiling HNO_3 and an aliquot of this solution was used to assay the radioactivity. The measurements of radioactivity were made with a NaI crystal and a Nuclear-Chicago medical spectrometer (model 132).

Fig. 1 shows a practically complete inhibition of octanoate oxidation by liver mitochondria obtained from rats killed 2 days after the administration of stable

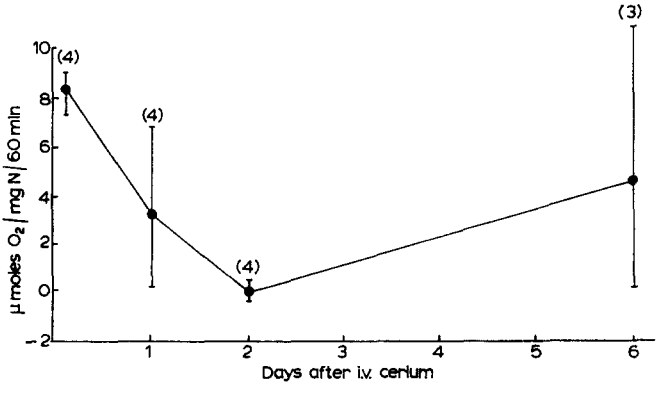

Fig. 1. Fatty acid oxidation in cerium (2 mg/kg)-treated rats. All animals fasted 24 h before being killed. The number of rats used for each determination is shown in the parenthesis. The mean value is represented by the solid circles and the range is indicated by the vertical bar which passes through each mean value.

cerium. The wide range of values observed at 1 and 6 days is similar to the variation of liver lipids during the onset and recovery phases of fatty infiltration, respectively, in rats exposed to cerium[2]. The curve shown in Fig. 2 indicates that the cerium rapidly localizes in the liver (about 70 % of the dose injected) and it remains in the liver at the same high level, even though the liver fat returns to normal after a week[2]. The evidence shown here would imply that the development of the fatty liver and the recovery of the liver from the lipid infiltration depend on the ability of the mitochondrial fatty acid oxidizing systems to function properly. Furthermore, lipid mobilization from extrahepatic tissues appears to be a significant source of the abnormal accumulation of liver lipids after a single cerium injection[6].

The large metal concentration in the liver and the changes seen in the oxidase system do not at first glance seem to have any relationship; however, the action of cerium on the mitochondrial system studied could be modified if the chemical form of cerium in the liver were altered with time. At present we have no knowledge of

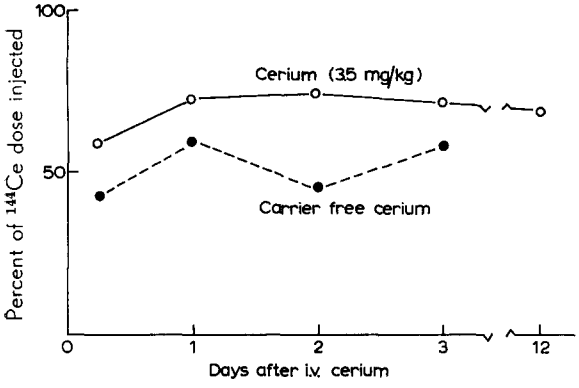

Fig. 2. Localization of cerium in rat liver. Each mean value represents data from 4 rats. The carrier-free cerium is the lowest carrier level of ^{144}Ce available from Oak Ridge National Laboratory (approx. 0.02 mg cerium/kg under the condition of these experiments).

what chemical form the cerium might have in the liver. It is well known that the rare earths form complexes with a wide variety of biological substances *in vitro*[10–12], but a better knowledge of the chemical nature of cerium *in vivo* is needed, especially under the conditions that produce fatty-liver degeneration. The work of BAMANN *et al.*[7–9] has emphasized the important "phosphatase-like" activity of many of the rare-earth metal hydroxides, including that of cerium. Whether dephosphorylation of mitochondrial nucleotides by cerium *in vivo* can explain the oxidative change reported here is a question that deserves attention.

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Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn. (U.S.A.)

FRED SNYDER
FRED BAKER
JOHN RAFTER
G. C. KYKER

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