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EFFECT OF VINCRISTINE ON TRITON WR-1339 INDUCED HYPERLIPIDEMIA IN MICE

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Abstract—The effect of Vincristine sulphate on the hyperlipidemia induced in mice by Triton WR-1339 was studied. A single i.p. dose (1 mg/kg) of Vincristine inhibited the development of hyperlipidemia within 2–4 hr. Vincristine sulphate seems to exert its lipid lowering effect through the liver by inhibiting either the synthesis or the excretion of lipoproteins or both.

THE EFFECT of various antitumor agents on the lipid metabolism of the organism has been little investigated. In our studies concerning the mechanism of action of Vincristine it was noted that a single intraperitoneal dose rapidly and strongly reduced the serum lipid content of normal rats, and the hyperlipidemia of animals bearing ascites tumors, while there was a simultaneous rise in the concentration of neutral (triglyceride) lipids in the liver.[1] In the present work the effect of Vincristine on Triton WR-1339 induced hyperlipidemia in mice was studied.

MATERIALS AND METHODS

Experimental hyperlipidemia was induced in non-fasted Swiss outbred male albino mice, weighing 30–35 g, by a single intraperitoneal dose of Triton WR-1339 (Winthrop Laboratories, Newcastle), a non-ionic detergent, in physiological saline solution. Schurr *et al.*[2] found the effective dose in rats to be 300–400 mg/kg. Preliminary experiments in mice revealed that a considerably larger dose, 900 mg/kg Triton WR-1339, is required to achieve the same effect.

The Triton-treated animals were divided into 2 groups of 11 animals each. The first, control group, served to demonstrate the development of hyperlipidemia as a result of Triton treatment. The second group of animals received a single intraperitoneal dose of 1 mg/kg Vincristine sulphate (G. Richter, Budapest) in the 4th hr following the Triton administration.

In 0, 2, 4, 6, 8, 12 and 24 hr after the administration of Triton (2, 4, 8, 20 hr after the Vincristine treatment) blood was drawn from the tail of the animals through a heparinized capillary. The total serum lipid concentration was measured by the colorimetric micromethod of Frings *et al.*[3] From 5 μl serum the main individual lipid fractions (cholesterol esters, triglycerides, free fatty acids, cholesterol, phospholipids) were separated by thin-layer chromatography and were determined by photodensitometry.[4–7] This technique enabled the lipid pattern of each animal to be monitored.

RESULTS AND DISCUSSION

In the course of the experiments it was observed that the single intraperitoneal dose of 900 mg/kg Triton produced within 24 hr a well reproducible hyperlipidemia in mice (Fig. 1). The rise in total serum lipid content was primarily due to the marked increase in triglycerides (Fig. 2). A similar, but more moderate rise was noted in the phospholipid, free fatty acid and free cholesterol levels of the serum (Figs. 3–5). The amount of cholesterol esters was not influenced by the Triton treatment (Fig. 6).

In the other group of experimental animals the intraperitoneally administered Vincristine sulphate was found to rapidly inhibit the development of Triton induced lipemia (2–4 hr, Fig. 1). Vincristine sulphate, inhibited primarily the accumulation of serum triglycerides (Fig. 2) but stabilized in a similar way the free fatty acid level (Fig. 3) and free cholesterol (Fig. 4). Vincristine sulphate was practically ineffective on cholesterol esters (Fig. 6).

Changes in the total lipid content of the serum and of the individual lipids studied reflect implicitly the changes in the lipoprotein fractions of the serum. Due to the masking effect of Triton, however, the distribution of serum lipoprotein could not be studied directly by the classic electrophoretic procedures (agarose-, polyacrylamide gel). The high triglyceride and free cholesterol levels and the almost unchanged concentrations of cholesterol esters, usually considered to be the main lipid constituents of low density lipoprotein, indicate that under the influence of Triton in the serum the very low density (VLDL) lipoprotein fractions accumulate and that Vincristine inhibits mainly their access into the circulation. The almost unchanged rise in phospholipids infers also to this fact (Fig. 3), these phospholipids are the main constituents of other lipoproteins (low density and high density lipoprotein).

It was previously ascertained that in intact animals and in case of tumor-induced

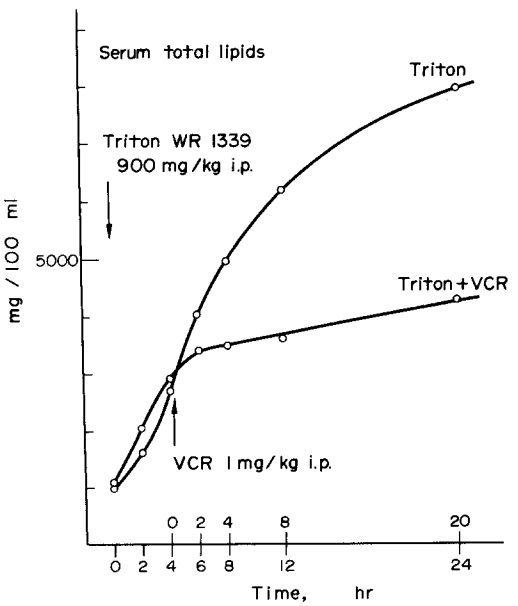

FIG. 1. Changes in the total lipid content of the serum after i.p. administration of Triton and Triton-Vincristine (VCR).

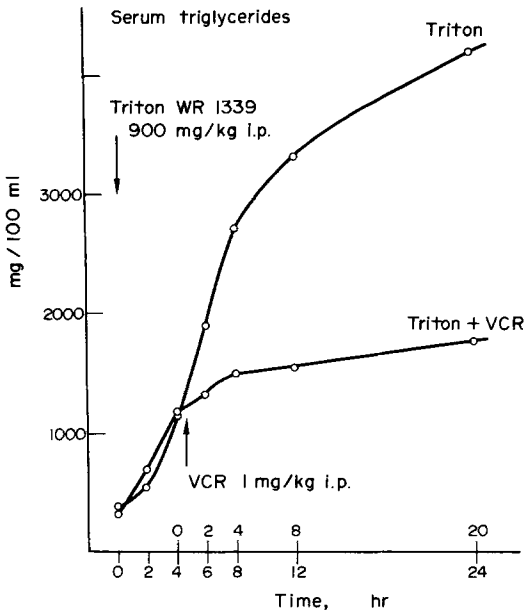

FIG. 2. Serum triglyceride concentrations after i.p. administration of Triton and Triton-Vincristine (VCR).

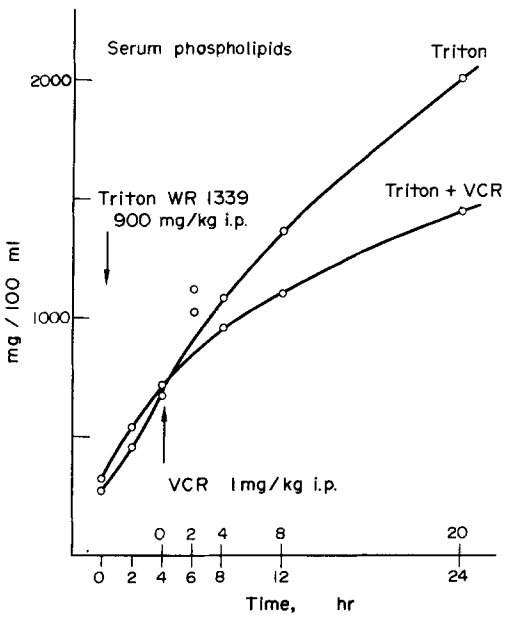

FIG. 3. Serum phospholipid concentrations after i.p. administration of Triton and Triton-Vincristine (VCR).

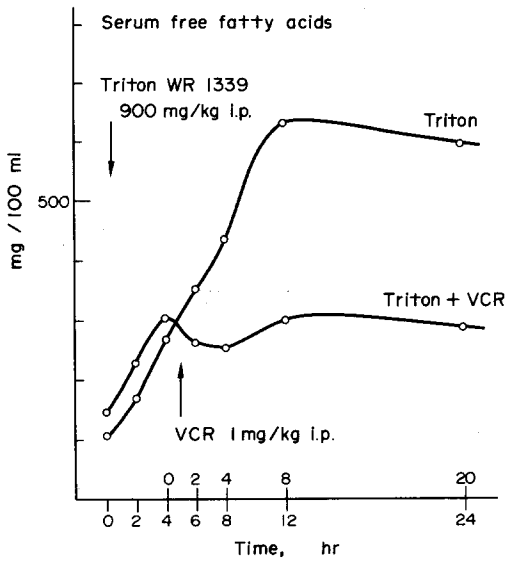

FIG. 4. Serum free fatty acid levels after i.p. administration of Triton and Triton-Vincristine (VCR).

hyperlipidemia Vincristine, even at low doses (0·1–0·2 mg/kg), reduces the amount of low density lipoproteins. In addition to the rapidity of the process the reversibility of the lipid reduction was also noteworthy after the excretion or decomposition of Vincristine.

As it is known Triton WR-1339 forms molecular complexes with the serum lipoproteins rendering them refractive to the action of lipolytic enzymes. It does not in-

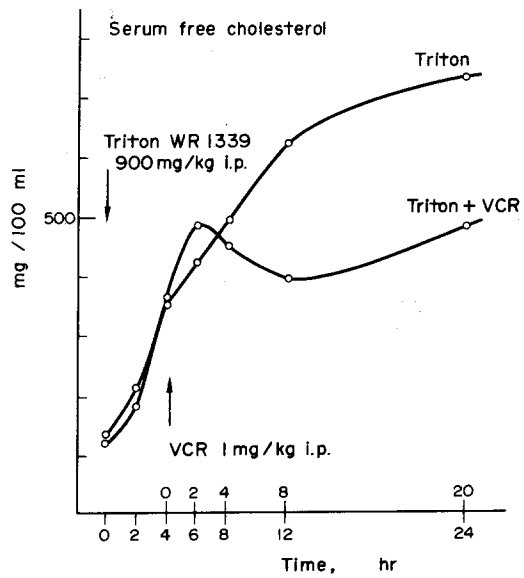

FIG. 5. Serum free cholesterol concentrations after i.p. administration of Triton and Triton-Vincristine (VCR).

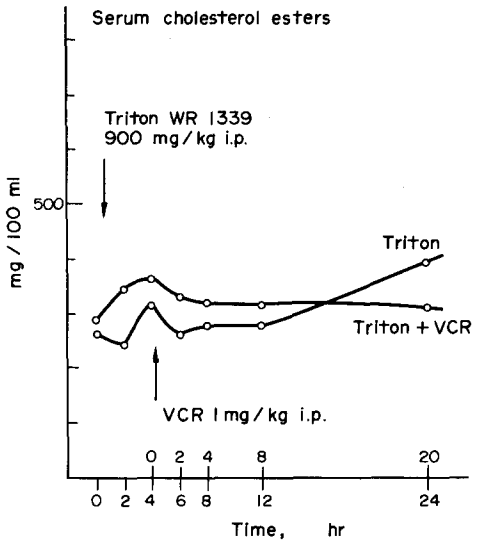

FIG. 6. Serum levels of esterified cholesterol after i.p. administration of Triton and Triton-Vincristine (VCR).

terfere with the lipoprotein synthesis of the liver[8] and the extent of Triton induced lipidemia can be evaluated as the triglyceride excretion index of the liver.[2]

On the basis of our studies it can be presumed that Vincristine exerts its lipid-reducing effect through the liver by inhibiting either the synthesis or the excretion of lipoproteins or both. Detailed clarification of the effect requires further studies.

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