INHIBITION OF DIETARY CHOLESTEROL ESTER ABSORPTION BY 3-BCP, A SUICIDE INHIBITOR OF CHOLESTEROL-ESTERASE. J. Martyn Bailey, Linda L. Gallo, and John Gillespie. Dept. of Biochemistry and Molecular Biology, George Washington University, School of Medicine, Washington, D.C.

Cholesterol esters, which can comprise over 75% of total cholesterol in diets rich in organ meats, must first be hydrolyzed by pancreatic cholesterol esterase (EC 3.1.1.13) before being absorbed (1). In its hydrolytic mode, catalysis by the enzyme involves a classical serine esterase mechanism in which the seroxide anion displaces the sterol moiety to give an acyl-enzyme intermediate, followed by nucleophilic displacement. In the absence of bile salt co-factor, the enzyme behaves like a simple esterase and readily hydrolyzes p-nitrophenyl acetate (2).

3-benzyl-6-chloropyrone (3-BCP) and 5-benzyl-6-chloropyrone (5-BCP) were synthesized as potential suicide inhibitors of the enzyme, according to the precedents of Katzenellenbogen (3,4).

Inhibition was selective, and pancreatic lipase was unaffected at concentrations up to 2 mM.

The ability of 3-BCP to inhibit cholesterol absorption when ingested as cholesterol ester was tested in Wistar Rats (300-400g) administered an intragastric emulsion containing 1\textsuperscript{H}-cholesterol oleate (280 mg, 50 $\mu$Ci), with or without the addition of 3-BCP (40 $\mu$moles). 1\textsuperscript{H}-cholesterol was assayed in blood samples taken at intervals for the next 24 hrs. (Figure 3).

The rate of absorption of cholesterol was reduced by an average of 60% in drug-treated animals.

In separate experiments, rats were administered a single dose of 3-BCP (40 $\mu$moles) in the same vehicle used to administer cholesterol oleate. After 5 hrs., the animals were killed and the intestinal enzyme activity assayed. Cholesterol esterase activity in intestinal lumen and mucosa was reduced 63% and 76% respectively by 3-BCP treatment. Body weights did not differ significantly in control and 3-BCP-treated animals during a 7 day post-treatment period.

Suicide inhibitors offer several potential advantages as therapeutic agents, since they are metabolically inert until activated by the target enzyme. The results described here demonstrate that a suicide inhibitor of cholesterol esterase that is functional in in vitro assays, can also display therapeutic effectiveness in vivo.

REFERENCES:

Supported by NIH grant # HL-33246