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The lipid-lowering agent gemfibrozil inhibits fatty acid esterification

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Gemfibrozil is a fibric acid derivative and plasma lipid lowering drug used in the treatment of hyperlipidaemia and atherosclerosis, conditions in which individuals have raised plasma lipid levels O'Connor *et al* (1990). In addition to increased plasma triglyceride clearance and increased levels of high density lipoproteins (HDL) this agent decreases the hepatic output of very low density lipoproteins (VLDL) Kesaniemi & Grundy (1984), Frick *et al* (1987). In achieving the latter gemfibrozil inhibits endogenous synthesis of the cholesterol and fatty acid components of VLDL Hemingway *et al* (1995) and stimulates the partitioning of fatty acids away from esterification and towards oxidation Lazarow & DeDuve (1976). Consequently, we have investigated the effect of gemfibrozil on glycerol-3-phosphate acyltransferase (GPAT), the regulatory enzyme of fatty acid esterification, in both white adipose tissue and liver. We have observed a significant inhibition of both white adipose tissue and liver microsomal GPAT in response to gemfibrozil treatment *in vivo*.

GPAT activity was measured in crude adipose tissue extracts, or in isolated liver microsomes, of control rats and rats treated with gemfibrozil (250mg/kg) for 2.5 hours. GPAT activity was assayed in the presence or absence of 10 mM N-Ethylmaleimide (NEM), a known inhibitor of microsomal GPAT activity Bates *et al* (1977), Coleman & Haynes (1983), and in the presence of 1.75 mg/ml bovine serum albumin (BSA) which is optimal for microsomal GPAT activity Bates & Saggerson (1977), Sugden *et al* (1980). The microsomal GPAT activity was taken to be the NEM-sensitive activity and in white adipose tissue extracts from gemfibrozil-treated rats a 49% decrease in microsomal GPAT activity was observed (Figure 1A). A similar 50% decrease in hepatic microsomal GPAT activity occurred in response to gemfibrozil treatment (Figure 1B).

These results suggest that gemfibrozil suppresses both white adipose tissue and liver triglyceride formation. The mechanism of GPAT inhibition by gemfibrozil is unknown. GPAT regulation by phosphorylation was reported by

Figure 1A - The Effect of Gemfibrozil on Microsomal GPAT Activity in White Adipose Tissue

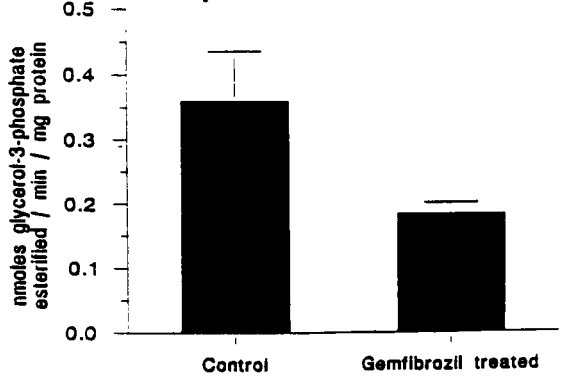
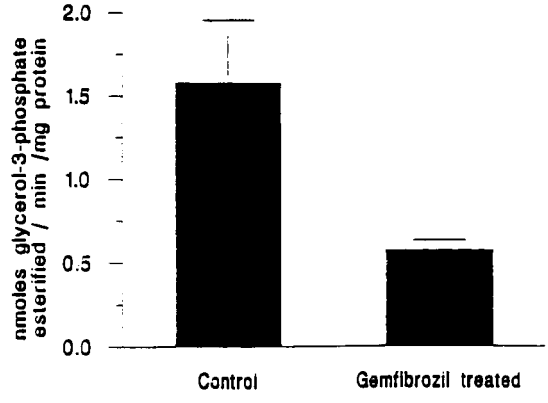


Figure 1B - The Effect of Gemfibrozil on Microsomal GPAT Activity in Liver



Nimmo & Houston (1978) and gemfibrozil has been shown to activate AMP-activated protein kinase Hemingway & Munday (1997). However, direct inhibition of GPAT, a decrease in GPAT concentration, or the displacement of the palmitoyl-CoA substrate are also possibilities.

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