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The effect of the lipid-lowering agent gemfibrozil on glucose handling

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The clinical manifestations of non-insulin dependent diabetes mellitus (NIDDM) predispose patients to atherosclerosis and coronary heart disease (CHD). Treatment may include the lipid-lowering agent gemfibrozil. However, there are conflicting reports with respect to the effects of gemfibrozil on glucose control in NIDDM patients. Some describe unaltered or improved glucose control Pagani *et al* (1989), while others report reduced insulin sensitivity, increased plasma glucose levels and glucose intolerance Samuel (1983), Konttinen *et al*, (1979), and that fibrates in high doses have been observed to produce glucose intolerance in non-diabetic patients. Gemfibrozil inhibits the hepatic conversion of carbohydrate precursors to the lipid components of VLDL Hemingway *et al* (1995), Hemingway & Munday (1997). If the homeostatic balance between fuel utilisation, fuel storage and fuel mobilisation is interrupted by gemfibrozil there could be important consequences for glucose handling, and carbohydrate metabolism in peripheral tissues.

The aim of this study was to investigate the effect of gemfibrozil administration *in vivo* on the aortic blood metabolite concentrations and hepatic glycogen content and synthesis. Blood metabolite levels were measured at D6 of the diurnal cycle in control rats and rats treated with gemfibrozil (250 mg/kg) for 150 min. The blood glucose concentration in control rats (Table 1.) was in general agreement with previously published values Williamson (1989), Hopkirk & Bloxham (1977). However, following gemfibrozil treatment there was a significant increase in blood glucose concentration (Table 1). Pyruvate and lactate concentrations in this study were the same or slightly higher than those measured previously by Robinson & Williamson (1977), Williamson *et al* (1983) and were unaffected by gemfibrozil (Table 1).

Hepatic glycogen content in control rats at D6 was found to be 298 μmol glycogen/g liver (Table 2) which is approaching the maximal physiological concentration of liver glycogen (~330 μmol/g), Stalmans *et al* (1987). The acute response to gemfibrozil treatment at the peak of feeding time (D6) was a significant increase in hepatic glycogen content (Table 2). A 66% increase in the rate of hepatic glycogen synthesis was also observed in response to gemfibrozil treatment (Table 2).

Table 1. The Effect of Gemfibrozil on Blood Metabolite Concentrations. The results are expressed as μmol of metabolite / ml blood. Values are ± S.E.M. with the number of observations in parentheses. Values that are significantly different (by an unpaired Student's t-test) from the control values are shown : * $P < 0.05$.

		Glucose	Lactate	Pyruvate
Control	(6)	6.69 ± 0.26	2.03 ± 0.10	0.17 ± 0.02
Gemfibrozil	(6)	7.69 ± 0.31*	1.89 ± 0.18	0.16 ± 0.03

Table 2. The Effect of Gemfibrozil on Hepatic Glycogen Content and Synthesis. Hepatic glycogen content is expressed as μmol glycogen / g liver and are ± S.E.M. with the number of observations in parentheses. Values that are significantly different (by an unpaired Student's t-test) from the control values are shown : * $P < 0.05$. The rates of hepatic glycogen synthesis are expressed as μmol ^3H_2O incorporated / μmol glycogen / hr.

	Glycogen Content	Glycogen Synthesis
Control	298.33 ± 5.39 (4)	0.18
Gemfibrozil	340.19 + 11.75* (4)	0.30

The data suggests that the liver attempted to store carbohydrate that was spared from lipid synthesis by gemfibrozil. However, plasma glucose still increased. This may have serious implications for the gemfibrozil-treatment of hyperlipidaemic patients with NIDDM. Further investigation into the mechanism of gemfibrozil induced antagonism of insulin action is required.

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