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Effects of Peroxisome Proliferators Gemfibrozil and Clofibrate on Syntheses of Dolichol and Cholesterol in Rat Liver

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The effects of two peroxisome proliferators, gemfibrozil and clofibrate, on syntheses of dolichol and cholesterol in rat liver were investigated. Gemfibrozil did not affect the overall content of dolichyl phosphate, but it changed the chain-length distribution of dolichyl phosphate, increasing the levels of species with shorter isoprene units. Gemfibrozil suppressed synthesis of dolichyl phosphate from [^{3}H]mevalonate and [^{3}H]farnesyl pyrophosphate in rat liver. In contrast, clofibrate increased the content of dolichol (free and acyl ester forms). It remarkably enhanced dolichol synthesis from mevalonate, but did not affect dolichol synthesis from farnesyl pyrophosphate. Gemfibrozil elevated cholesterol synthesis from [^{14}C]acetate, but did not affect the synthesis from mevalonate. Clofibrate suppressed cholesterol synthesis from acetate, but did not affect cholesterol synthesis from mevalonate. These results suggest that gemfibrozil suppresses synthesis of dolichyl phosphate by inhibiting, at the least, the pathway from farnesyl pyrophosphate to dolichyl phosphate. As a result, the chain-length pattern of dolichyl phosphate may show an increase in shorter isoprene units. Clofibrate may increase the content of dolichol by enhancing dolichol synthesis from mevalonate. Gemfibrozil may increase cholesterol synthesis by activating the pathway from acetate to mevalonate. Unlike gemfibrozil, clofibrate may decrease cholesterol synthesis by inhibiting the pathway from acetate to mevalonate.