What factors control hepatic triacylglycerol accumulation in alcohol abuse?

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Introduction
It is well known that ethanol stimulates the synthesis and the accumulation of triacylglycerols in the liver (Hawkins & Kalant, 1972; Lieber, 1974; Kondrup et al., 1979). The following discussion will try to identify how this increased esterification of fatty acids is brought about in terms of what is known about the control of hepatic triacylglycerol synthesis.

Changes in enzyme activities associated with triacylglycerol synthesis

The administration of an acute dose of ethanol to rats or hamsters produces increases in the hepatic activity of phosphatidate phosphohydrolase (Fig. 1) of 2–7-fold within 4–10 h (Savolainen, 1977; Pritchard et al., 1977; Lamb et al., 1979). This increase is specific for the phosphohydrolase since there were no significant changes in the activities of other enzymes that are involved directly in triacylglycerol synthesis (Pritchard et al., 1977; Björkhem & Östling, 1979). The changes in the activity of phosphatidate phosphohydrolase appeared to result from the increase in the concentration of corticosterone relative to insulin in the blood of the rats. Similar effects can be observed with other nutrients such as fructose, sorbitol and glycerol (Brindley et al., 1979a).

The importance of the glucocorticoid release is emphasized by the fact that the increase of 6.9-fold that was produced by ethanol after 7 h in normal rats was decreased to 1.7-fold in rats that had been adrenalectomized (Brindley et al., 1979a). Furthermore, pretreatment of the rats with the drug benfluorex, decreased the rise in circulating corticosterone, the increase in the phosphohydrolase activity, and the ethanol-induced stimulation of the synthesis and accumulation of triacylglycerols in the liver (Pritchard et al., 1977, 1979; Brindley et al., 1979b). Benfluorex is a hypolipaemic and an antihyperglycaemic agent that is able to decrease the effects of several stimuli that provoke metabolic stress responses (Brindley, 1988). It is believed to act through the serotonergic system. Ethanol is thought to be able to increase the concentration of circulating corticosterone by stimulating the central serotonergic system (Brick & Pohorecky, 1985) and benfluorex may act by blocking this system (Brindley, 1988). The effect of ethanol in increasing the concentration of corticosterone in rats is exaggerated when they are fed diets enriched in fat (Brindley et al., 1981). This may partly explain why high fat diets exaggerate the effect of ethanol in producing a fatty liver. It is relevant to note that an intact hypothalamic pituitary adrenal axis is required for ethanol to produce a fatty liver (Brodie & Maickel, 1963; Maickel & Brodic, 1963; Maling et al., 1963).

The residual increase in phosphatidate phosphohydrolase activity that is produced by an acute dose of ethanol in adrenalectomized rats (Brindley et al., 1979a,b) might have been caused by an increased concentration of glucagon in the blood (Tieno et al., 1974) resulting in an increase in cyclic AMP concentrations in the liver (Jauhonen et al., 1975). Cyclic AMP causes a long-term increase in phosphatidate phosphohydrolase activity in the liver which probably results from an increase in its synthesis (Pittner et al., 1985a,b) and stability (Pittner et al., 1986).

Chronic administration of ethanol to hamsters (Lamb et al., 1979) and baboons (Savolainen et al., 1984) also increases phosphatidate phosphohydrolase activity. This was also accompanied in the latter case with an increased activity of diacylglycerol acyltransferase.

Consequently, there is a general agreement that phosphatidate phosphohydrolase increases after acute and chronic ethanol consumption. The increase in this activity together with the chronic increase in diacylglycerol acyltransferase would increase the potential of the liver to synthesize triacylglycerol. The expression of this potential depends upon the substrate supply to the liver (Brindley, 1984, 1988). For example, the cytosolic phosphatidate phosphohydrolase is thought to be metabolically inactive and its translocation to the endoplasmic reticulum causes this activity to be expressed (Brindley, 1984, 1988). This is mainly brought about by an accumulation of fatty acids and their CoA esters in the liver. The presence of a higher phosphohydrolase in the liver also means that more of the enzyme should be associated with the endoplasmic reticulum at a given concentration of fatty acid (Pittner et al., 1985a,b).

Abbreviations used: VLDL, very low density lipoprotein.
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Effects of ethanol on the availability of substrates for hepatic triacylglycerol synthesis

Ethanol increased the availability of precursors for hepatic triacylglycerol synthesis in several ways. First, ethanol can increase the blood flow to the liver and thereby increase the relative extraction and use of fatty acids relative to other organs (Abrams & Cooper, 1976a,b). Furthermore, ethanol itself can provoke a 'stress reaction' thus stimulating lipolysis in adipose tissue and increasing the fatty acid concentration in the blood (Pohorecky, 1984; Brick & Pohorecky, 1985).

The alternative source of exogenous fatty acids for the liver is from the uptake of chylomicron remnants (Fig. 1) and undoubtedly dietary fat serves as a major precursor for the triacylglycerol that accumulates in the liver (Lieber, 1974). However, there is evidence that the clearance of the chylomicron remnants by the liver can be impaired by ethanol and that this can contribute to the hyperlipidaemia that is observed (Redgrave & Martin, 1977).

Ethanol also decreases the catabolism of fatty acids subsequent to their uptake by the liver. Ethanol is rapidly oxidized to acetaldehyde and acetate by dehydrogenases that produce NADH. This provides the hepatocyte with a copious supply of energy through electron transport and spares the use of other fuels such as glucose and fatty acids. The major decrease in β-oxidation is seen at the level of the production of CO₂ via the citric acid cycle with a smaller effect on the rate of ketogenesis (Fellenius & Kiessling, 1973; Kondrup et al., 1979; Wiebe & Belfrage, 1980). The increased availability of acetate could provide the precursor for fatty acid synthesis which is stimulated by ethanol (Cascales et al., 1983). However, in reality this process is only a minor contributor of fatty acids in producing the steatosis (Hawkins & Kalant, 1972; Konrad & Reed, 1977).

The other direct precursor for the synthesis of triacylglycerols is glycerol phosphate (Fig. 1) and its concentration in the liver is increased by ethanol as a result of ethanol oxidation and the changes in redox state (Lieber, 1974). However, it is not at all clear that the oxidation of the ethanol and the subsequent change in redox state is an important factor in causing the steatosis (Kalant et al., 1972; Fellenius et al., 1973; Estler, 1974; Abrams & Cooper, 1976a). Glycerol phosphate can become rate-limiting in the synthesis of hepatic triacylglycerols in the liver especially when the fatty acid availability is high (Fellenius et al., 1973) or when glucagon becomes a major factor in regulating hepatic metabolism (De Clercq et al., 1982). Therefore, the increased provision of glycerol phosphate caused by the changes in redox state would at least help to prevent this substrate becoming ratelimiting.

It has been suggested that the changes in redox state could also be important in increasing the activity of phosphatidate phosphohydrolase (Savolainen & Hassinen, 1978). This is supported by the observation that pyrazole, which inhibits alcohol dehydrogenase, can partially prevent the ethanol-induced increase in the phosphatidate phosphohydrolase activity in cultured hepatocytes (Wood & Lamb, 1978). In vivo, the situation is more complicated. Pyrazole has been shown to partially prevent the ethanol-induced increase in phosphatidate phosphohydrolase activity (Savolainen & Hassinen, 1980; Ide & Nakazawa, 1987). However, other work has shown that ethanol-induced increases in hepatic phosphatidate phosphohydrolase can be obtained even though the changes in hepatic redox state had been blocked with pyrazole (Hassinen et al., 1979). Moreover, part of the observed effect of pyrazole in preventing the rise in the phosphatidate phosphohydrolase activity appeared to be related to the consequent decrease in the synthesis of acetaldehyde (Ide & Nakazawa, 1987).

These combined results appear to confirm that the stress reaction produced by the accumulation of ethanol and acetaldehyde is an important component in increasing phosphatidate phosphohydrolase activity and the steatosis in addition to any effects that the changes in redox state may have.

Effects of ethanol on very low density lipoprotein secretion

It is possible that the steatosis produced by ethanol could partly result from a decreased release of very low density lipoprotein secretion.
lipoprotein (VLDL) from the liver, and evidence for this has been obtained (Lieber, 1974; Estler, 1975). It is likely that a decreased secretion of triacylglycerol from the liver is more important at high doses of ethanol and that this is caused by the hepatotoxic effects of ethanol and acetaldehyde. However, ethanol can also stimulate the secretion of VLDL (Hernell & Johnson, 1973; Lieber, 1974; Mårtland & Öjé, 1974; Titov & Pitsin, 1978), and alcohol consumption is normally associated with a hypertriglyceridaemia especially in the fed condition. The effect of glucocorticoids in stimulating VLDL secretion (Mangiapane & Brindley, 1986) may be important in this respect. It therefore seems that ethanol stimulates the incorporation of nutrients into triacylglycerols by the liver and that this results in higher levels of VLDL secretion as long as the ethanol dose is not high enough to decrease this secretion. In most cases an impaired secretion is unlikely to be a major factor in causing the steatosis.

Conclusion

The effects of ethanol in producing a fatty liver result from a complex interaction of changes in hormonal status, enzyme activities and in substrate supply. In low doses, ethanol can have a protective effect against stress reactions (Brick & Pohorecky, 1982). However, in higher doses it produces a stress type of reaction that can be seen biochemically in the increased concentrations of circulating glucocorticoids, glucagon, catecholamines and fatty acids. The release of glucagon and glucocorticoids increases the activity of phosphatidate phosphohydrolase in the liver within hours. Chronic ethanol administration can also increase the activity of diacylglycerol acyltransferase. These enzyme changes increase the potential of the liver to synthesize triacylglycerols. However, the expression of this potential relies upon the ability of ethanol to increase the availability of substrates to triacylglycerol synthesis such as glycerol phosphate and fatty acids in the liver.

Received 11 December 1987

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Hernell, O. & Johnson, O. (1973) Lipids 8, 503-508


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