Intrahepatic proteolysis is a major determinant of secretion of ApoB-containing lipoproteins into plasma. Stimulation of post-ER presecretory proteolysis (PERPP) of ApoB by n-3 polyunsaturated fatty acids has been found to result in reduced secretion of VLDL particles by hepatocytes. A new study has shown that this stimulation is promoted by pro-oxidant conditions that result in increased hepatic lipid hydroperoxide content (see the related article beginning on page 1277). Conversely, PERPP is suppressed by antioxidants and by saturated fatty acids, which are not susceptible to lipid peroxidation. Hence reduction of oxidative stress may have the unexpected side effect of increasing plasma lipid levels.

Dietary fats with differing fatty acid composition can influence plasma lipid levels by modulating hepatic production and clearance of lipoproteins (1), as well as by altering activity of cholesteryl ester transfer protein (2). Suppression and stimulation of hepatic LDL receptor activity are major determinants, respectively, of the effects of saturated and polyunsaturated fatty acids on plasma LDL clearance (1), but the mechanisms for effects of specific fatty acids on hepatic lipoprotein production are less well understood. This is in large part due to the multiple influences of fatty acids on processes that regulate hepatic lipid production and storage, and processing of ApoB in conjunction with lipoprotein synthesis and secretion (3).

Fatty acids are critically involved in hepatic lipoprotein production pathways that help maintain hepatic cholesterol homeostasis and the ability to respond to energy and other metabolic needs. Triacylglycerides influence a critical early step in secretion of ApoB-containing lipoproteins, namely the cotranslational binding of lipids to ApoB in the ER mediated by microsomal triglyceride transfer protein (MTP). The resulting protection of specific ApoB domains from proteolysis, termed ER-associated degradation (ERAD), leads either to secretion of a relatively lipid-depleted particle or to further, posttranslational lipidation (3) (Figure 1). The latter may occur in a graded manner in the ER, the vesicular tubular complex, and/or the Golgi apparatus, or by fusion with a preformed lipid droplet in the ER by a process that is not dependent on MTP.

Post-ER presecretory proteolysis and hepatic lipid hydroperoxide content
Recently, Fisher et al. have identified another degradative process that can modulate hepatic secretion of more mature ApoB-containing lipoproteins (4). They have found that inhibition of hepatic ApoB secretion by n-3 polyunsaturated fatty acids occurs via activation of this process, which has been designated post-ER presecretory proteolysis (PERPP) (4). In this issue of the JCI, Pan, Fisher, and colleagues have now shown, using several lines of evidence, that this effect is mediated by fatty acid peroxidation, and that it also occurs with n-6 polyunsaturated fatty acids (5). Moreover, the finding that ApoB degradation is stimulated by pro-oxidant conditions and inhibited by antioxidants raises the question of whether variation in intrahepatic oxidative stress contributes to physiologic and/or pathologic modulation of ApoB-containing lipoprotein metabolism. There is indeed abundant evidence that consumption of supplements of longer-chain n-3 marine-derived polyunsaturated fatty acids (eicosapentaenoic and docosahexaenoic acids) can lower plasma triglyceride and VLDL levels in humans (6). Recently, it has been shown that population variation in dietary intake of a plant-derived n-3 polyunsaturated fatty acid, linolenic acid, is significantly associated with plasma triglyceride levels, independent of other nutrients, including longer-chain n-3 polyunsaturated fatty acids (7). As Pan et al. point out, however, in their study linolenic acid suppressed ApoB secretion from rat hepatoma cells to a greater extent than could be accounted for by the relation of secretion to intrahepatic lipid hydroperoxide content as assessed by levels of thiobarbituric acid–reactive substances (TBARSs) (5). It should be noted, however, that TBARSs do not represent the full spectrum of products of lipid peroxidation, such as F2-isoprostanes. Moreover, despite the capacity for peroxidation of both n-3 and n-6 polyunsaturated fatty acids, the latter have minimal and generally non-significant effects on plasma triglyceride levels in humans (8). Hence increased lipid peroxidation of n-3 fatty acids does not fully explain the effects of these fatty acids on hepatic ApoB-containing lipoprotein secretion. Other effects, such as reduced lipid synthesis, may also play a role.

Oxidative stress and modulation of pathways for hepatic lipoprotein secretion
The direct relation of the number of unsaturated bonds to lipid peroxidation is consistent with the lack of a suppressive effect of saturated fatty acids on plasma triglyceride levels. In contrast, a saturated fatty acid, myristic acid, was found to stimulate secretion of ApoB-containing lipoproteins.
lipoproteins from liver cells in conjunction with protection from a proteolytic process consistent with PERPP (9). Interestingly, the secreted lipoproteins under these conditions were denser than VLDLs and were more triglyceride-depleted than those secreted in the presence of albumin or oleic acid. This suggests that differences in conformation or composition of newly synthesized ApoB-containing lipoproteins can alter their exposure to PERPP in such a way that smaller, triglyceride-depleted particles formed under the influence of saturated fatty acids tend to escape this process, while larger, triglyceride-rich VLDLs are more susceptible. However, the results of Pan et al. (5) indicate that the stimulation of lipoprotein secretion by myristic acid is disproportionately greater than would be predicted by reduced hepatic TBARS content, suggesting, as was the case with linolenic acid, that effects other than those related to lipid peroxidation are involved. Many questions remain as to the nature and physiologic importance of the PERPP system, the properties of lipoproteins that affect their susceptibility to PERPP, the mechanisms by which dietary fatty acids can affect this susceptibility, and the means by which oxidation products can suppress PERPP. It will be particularly challenging to assess the extent to which these mechanisms may influence metabolism of ApoB-containing lipoproteins in humans. However, clues may be found in evidence that levels and distribution of LDL subspecies can serve as markers for intrahepatic pathways that result in formation of different hepatic secretory products (10) (Figure 1).

We have found that increased intake of saturated fatty acids is associated with higher levels of larger, more buoyant LDL particles (11). The concentrations of large, buoyant LDL particles are inversely related to plasma VLDL levels (12). Lipoprotein kinetic studies in humans have indicated that reduced plasma triglyceride and VLDL levels are correlated with the extent of direct secretion of IDLs and LDLs into plasma (13). Hence, one might surmise (Figure 1) that increased intake of cholesterol-raising saturated fatty acids increases direct hepatic secretion of IDLs and large LDLs, a process consistent with the evi-
Dysbindin-1 and schizophrenia: from genetics to neuropathology

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The gene encoding dysbindin-1 has recently been implicated in susceptibility to schizophrenia. In this issue of the *JCI*, Talbot et al. show that, contrary to expectations, dysbindin-1 is located presynaptically in glutamatergic neurons and is reduced at these locations in schizophrenia (see the related article beginning on page 1353). Further studies of dysbindin-1 and the proteins with which it interacts can be expected to throw light on the pathogenesis of schizophrenia.

Schizophrenia is a common, severely disabling, mental disorder (1), and understanding its etiology and pathogenesis is one of the most important challenges facing psychiatry. Despite great endeavor, achieving this has proven difficult given the absence of a diagnostic neuropathology or biological markers, and few clear insights have emerged. However, there is currently a consensus that the disorder is, at least in part, neurodevelopmental (2). At the structural level, there are reductions in the neocortex and neuronal size that are widespread but not uniform, with temporal lobe structures, notably the hippocampal formation (HF), particularly affected (3). These changes in turn probably result from alterations in synaptic, dendritic, and axonal organization (3). At the functional level, accumulating evidence also implicates altered glutamate

citations

**Commentaries**


Nonstandard abbreviations used: hippocampal formation (HF).

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