Brief Review

The Adipocyte, Fatty Acid Trapping, and Atherogenesis

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Much effort has been spent to identify the factors that contribute to coronary artery disease. Not surprisingly, adipose tissue has gained little attention to date in this search because no immediate and critical links between adipocyte metabolism and atherogenesis may be evident to most people. But coronary artery disease is a public health problem only in societies with high fatty acid intakes; therefore, our purpose is to outline a hypothesis that adipose tissue dysfunction may be a very common—indeed, perhaps even the most common—cause of the dyslipoproteinemia and insulin resistance that so frequently lead to coronary disease. This complex and multifaceted syndrome has received many names, depending on the original point of interest. Amongst these names are hyperapoB, familial combined hyperlipidemia, syndrome X, the plurimetabolic syndrome, the visceral fat syndrome, familial dyslipidemic hypertension, the atherogenic lipoprotein phenotype, and the deadly quartet. Whether these titles are caused by increased lipolysis has been the only mechanism suggested to link adipocyte dysfunction and dyslipidemia. In our opinion, although excess lipolysis may be of importance in certain situations, it is not likely to be the sole link between adipose tissue dysfunction and atherosclerosis. The hypothesis that will be outlined herein differs substantially from the current views and is based on the metabolic insights that have been gained from the recent recognition of the ASP pathway.

Along with insulin, ASP is a principal determinant of the rate of triglyceride synthesis in adipocytes and therefore is a principal determinant of the rate of fatty acid uptake or, as we shall describe it herein, fatty acid trapping by adipocytes. In brief, we postulate that failure to trap the normal proportion of dietary fatty acids in adipocytes leads to their abnormal diversion to liver and muscle, and from this abnormal diversion stems the complex array of metabolic alterations listed above that so markedly increase the risk of vascular disease in these patients.

The ASP Pathway

To outline our hypothesis, we first must review the major features of the ASP pathway. Adipocytes synthesize triglyceride from the fatty acids delivered to them by the triglyceriderich lipoproteins, chylomicrons, and VLDL, and the triglyceride in adipocytes constitutes the energy store from which fatty acids are released as needed. Thus, the processes that regulate the rate at which adipocytes store and release energy are of considerable interest. The rate of both of these is determined, in large part, by the ASP pathway, which is constituted as follows. Adipocytes synthesize and secrete the three proteins of the alternate complement pathway: the third component of complement (C3), factor B, and factor D (or adipsin). These proteins interact to produce a 77-amino acid fragment of C3, the terminal arginine of which is removed by carboxypeptidases to produce ASP.

The two most potent in vitro stimulants of triglyceride synthesis in adipocytes are insulin and ASP. Interestingly, the stimulatory effects of ASP are independent of and additive to those of insulin. ASP achieves its effect by increasing the activity of diacylglycerol acyltransferase, the last enzyme involved in the synthesis of a triglyceride molecule. ASP also increases specific membrane transport of glucose by stimulating the translocation of glucose transporters from the cytosol to the cell membrane, a mechanism that is identical to but independent of insulin.

As human adipocytes differentiate, they develop the capacity to synthesize the precursors of ASP, and as they enlarge, their capacity to synthesize ASP increases in parallel. Moreover, during differentiation, their capacity to synthesize triglyceride increases, and importantly, so does their response to ASP. Adipocytes from obese subjects remain responsive to ASP. By contrast, larger adipocytes are less responsive to insulin than smaller ones. Thus, insulin and ASP share features in common, but they also differ in important aspects.

The ASP Pathway and Trapping of Fatty Acids by Adipocytes

To trap dietary fatty acids in adipocytes, two things must happen in sequence (Fig 1). First, the fatty acids must be...
released from chylomicron triglyceride by the action of LPL.21

Next, and critically, these fatty acids must be taken up by the adipocyte and incorporated into triglyceride. The rate at which LPL can hydrolyze lipoprotein triglycerides is determined, in the first instance, by the number of active LPL molecules in contact with that particle, but it is also determined by the rate at which the fatty acids that are liberated can be removed from the capillary microenvironment. If they are not (Fig 2), then capillary fatty acid concentrations will rise abnormally, LPL activity will be product inhibited,22 and lipolysis will be reduced. In addition, the chylomicron particles and LPL will be prematurely detached from the endothelial surface before the normal amount of triglyceride has been removed from them, producing a triglyceride–rich chylomicron remnant.23,24

Much evidence now exists that the rate at which chylomicron triglycerides are hydrolyzed is not determined by the mass of LPL itself, the enzyme under most circumstances being present in excess of need.25 As the primary determinants of the rate of adipocyte triglyceride synthesis, ASP and insulin control the rate at which the fatty acids released from the chylomicron particle can be trapped by the adipocyte. Fatty acids that do not enter the adipocyte enter the general circulation, from which they reach the liver. Chylomicron remnants also are removed by the liver, the triglyceride they contain contributing to the hepatic fatty acid flux. There is, therefore, necessarily an inverse relation between the fatty acids trapped by the adipocyte and the fatty acids received by the liver and muscle. Under normal circumstances (Fig 1), approximately half of the fatty acids released from chylomicrons are trapped immediately by adipocytes, and half enter the general circulation.26 If fatty acid trapping is reduced (Fig 2), a smaller proportion of fatty acids from chylomicrons will enter adipocytes and a larger proportion, as fatty acids or triglyceride–rich chylomicron remnants, will enter the systemic circulation again.

All the adverse consequences predicted to occur from decreased fatty acid trapping by adipocytes have in fact been shown to occur frequently in patients with increased plasma apo B (Fig 3). Fasting plasma fatty acid levels are often elevated,27 and postprandially, they often rise abnormally as well.28 Postprandial plasma triglyceride clearance is prolonged,29 and chylomicron remnants accumulate in plasma.30 VLDL secretion is increased,31 presumably secondary to increased delivery of triglyceride–rich remnants and fatty acids to the liver.32 Because VLDL secretion is increased, production of LDL particles,33 many of which are smaller and denser than normal34 due to increased core lipid exchange, is increased. Increased core lipid exchange is anticipated from the increased secretion rate of VLDL particles, the hypertriglyceridemia, and the increased fatty acid concentrations35 that are present. Increased cholesterol ester–triglyceride exchange also may explain why the HDL cholesterol levels are often reduced as well.

Insulin resistance is among the most important of the multiple abnormalities in the hyperapoB syndrome.37 Multiple mechanisms might be responsible. Clearest among these are the documented effects of fatty acid on insulin and glucose metabolism. Fatty acids compete with glucose for entry and oxidation by muscle.36 They also impede insulin extraction by the liver37 and stimulate hepatic gluconeogenesis.38 Given the in vitro data that indicate ASP affects glucose transport in skeletal muscle,15 reduced responsiveness to ASP would be expected to reduce both fatty acid and glucose extraction by this tissue. Whatever the exact mechanism(s) responsible, it appears that reduced fatty acid trapping can account for all of
the metabolic manifestations of the hyperapoB/insulin resistance syndrome.

In the scenario outlined above, the increased secretion of VLDL particles represents a response of the liver to increased delivery of fatty acids, and although the exact mechanisms governing this response remain to be elucidated in detail, there is, at this point, overwhelming experimental evidence supporting the linkage between increased delivery of fatty acids and increased output of VLDL particles. It is also important to point out that ASP seems to have little direct effect on the liver, indicating that regulation of triglyceride synthesis in peripheral tissues caused by impaired response to ASP does not predict a reduced rate of hepatic triglyceride synthesis.

To be sure, there are many other factors, insulin important among them, that influence the rate and composition of apo B-100 particles secreted by the liver that we will not consider here. And we would stress that multiple defects exist, other than reduced fatty acid trapping, that can produce increased secretion of hepatic apo B-100 particles. From a pathophysiological viewpoint, however, it is interesting to note that many of these, along with increased delivery of fatty acids to the liver, share the consequence of increasing the mass of cholesterol ester within the liver, suggesting a final common pathway, at least for this series of disorders, that leads to increased secretion of hepatic apo B-100 particles.

Clinical Causes of Reduced Fatty Acid Trapping

Two clinical causes of reduced fatty acid trapping now seem likely. The first is a fault in the ASP receptor, and the second is omental obesity. ASP activates adipocyte triglyceride synthesis secondary to activation of a protein kinase C signal transduction pathway after specific interaction with a cell membrane receptor, and studies of cultured skin fibroblasts that used radiolabeled ASP in normal subjects have shown that stimulation of triglyceride synthesis is proportionate to specific binding of ASP to cell membrane. Furthermore, such studies have documented substantially reduced specific binding in patients with hyperapoB, resulting in markedly reduced stimulation of triglyceride synthesis. Moreover, adipocytes from patients with hyperapoB have reduced rates of triglyceride synthesis compared with adipocytes from normal subjects.

Taken together, these data point to a defective ASP receptor being present in a substantial proportion of patients with hyperapoB. A defective ASP receptor would result in reduced fatty acid trapping by the adipocyte, and this reduction would result, by the mechanisms outlined above (Figs 2 and 3), in the abnormalities that characterize the syndrome. Of importance, Reynisdottir et al have now shown that the alternate hypothesis, namely, increased fatty acid release due to increased adipocyte lipolysis, does not explain the metabolic abnormalities in patients with familial combined hyperlipidemia because their lipolytic responses and indeed the mass of hormone-sensitive lipase in their adipocytes are both reduced, not increased. If ASP plays the same role in regulating reuptake of fatty acids released from adipocytes as it does in promoting esterification of fatty acids derived from triglyceride–rich lipoproteins, then decreased effectiveness of the ASP pathway will result in increased fatty acid release from adipocytes without any change in intrinsic adipocyte lipolytic activity.

Individuals with omental obesity also frequently manifest all the features of this syndrome, and the pathogenesis in these individuals may follow much the same route. Regional differences in adipocyte function have been documented. Lipolysis seems to be greater in omental than in subcutaneous adipocytes, and this finding would tend to increase fatty acid flux to the liver. On the other hand, triglyceride synthesis has also been shown to be less in omental than in subcutaneous adipocytes, and this would result in reduced fatty acid trapping in these cells. Although the metabolic basis for this reduced triglyceride synthetic capacity remains to be established definitively, if adipocyte fatty acid trapping is reduced, the same broad sequence of metabolic consequences can be anticipated in omental obesity as in ASP receptor–defective hyperapoB.

Is it not, however, a contradiction in terms to hypothesize that obesity may be associated with impaired triglyceride synthesis? We would state not, because the distinction must be made between the short-term and long-term fates of fatty acids that are ingested or synthesized in excess of metabolic need. Consider first an obese individual with a normal ASP pathway and therefore normal fatty acid trapping. As illustrated in Fig 4, after the fat load, the majority of the dietary fatty acids are trapped in the adipocyte, the mass of these cells increasing in consequence. However, relatively little of the dietary fatty acid reaches the liver. After the meal, the needs of skeletal muscle and other tissues for fatty acids are met primarily by output of fatty acids from the adipocyte. Output of triglyceride from the liver in VLDL is modest because delivery was limited. There is, therefore, a net influx of fatty acids to adipose tissue during the meal and a net efflux after the meal, the size of the adipose tissue mass varying as these occur. Nevertheless, if net intake or synthesis of fatty acids exceeds net oxidation or incorporation into other biomolecules, adipose tissue mass will increase because it is the only tissue with the capacity to store increasing amounts of triglyceride.
Now consider an obese individual with reduced fatty acid trapping. As shown in Fig 4, compared with the obesity with normal fatty acid trapping, less of the dietary fatty acids are immediately deposited into adipose tissue in the early postprandial period, relatively more arriving at the liver. Therefore, during this time, adipose tissue triglyceride mass will increase less than in the obese individual with normal fatty acid trapping, whereas triglyceride mass in the liver will increase more than in the normal individual. During and after the meal, however, VLDL triglyceride output will be increased to avoid excessive triglyceride deposition in the liver. Part of this VLDL triglyceride will be used by muscle, but the excess will be presented to the adipocyte. VLDL allows, therefore, a second chance to deposit the fatty acids within the adipocyte. Therefore, just as in the normal individual, fatty acids in excess of metabolic need will be deposited in adipose tissue. This conclusion follows because the ASP pathway and insulin determine the rate of adipocyte triglyceride synthesis, not whether fatty acids will eventually be deposited in this tissue. The difference between normal and reduced fatty acid trapping relates not to the ultimate destination of the fatty acids but to how many turns of the metabolic wheel are required for the excess fatty acids to reach the one site of storage: adipose tissue. In summary, we present the hypothesis that the adipocyte may play a much larger role in the genesis of the common atherogenic dyslipoproteinemias than previously considered. We specifically postulate that this role relates to reduced fatty acid trapping caused by defective functioning of the ASP pathway. We have focused here on the ASP pathway, but the model of fatty acid trapping will apply also to insulin, whose role in adipose tissue metabolism has been appreciated for much longer. As does ASP, insulin stimulates triglyceride synthesis, and insulin resistance, therefore, will result in decreased fatty acid uptake as well as increased fatty acid release. Obviously, much remains to be learned about the regulation of fatty acid transport, storage, and utilization, and the hypotheses presented here need to be tested directly. Experiments in appropriate transgenic models are obviously of crucial significance. Nevertheless, the concepts presented fit well, we believe, with the tight epidemiological links between dietary fatty acid intake and the societal incidence of coronary artery disease and provide a framework in which to reconsider old observations, to reevaluate present dogma, and to generate new experimental approaches.

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References


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