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Diacylglycerol acyltransferases: Potential roles as pharmacological targets

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TG, triglycerides;
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VLDL, very low density lipoprotein;
DGAT, diacylglycerol acyltransferase;
MTP, microsomal transfer protein

ABSTRACT

Triglyceride (TG) synthesis occurs in many cell-types, but only the adipocyte is specialised for TG storage. The increased incidence of obesity and its attendant pathologies have increased interest in pharmacological strategies aimed at inhibition of triglyceride synthesis. In the liver this would also appear to offer the advantages of the prevention of steatosis and/or dyslipidaemia. The two major enzymes that have DGAT activity appear to have specialised functions, that are most evident in triglyceride-secreting tissues. The presence of triglyceride in non-adipose cells can lead to (through lipolysis), or be a marker for, undesirable complications such as insulin resistance, or can be indicative of simultaneously high capacities for triglyceride synthesis, lipolysis and oxidation of fatty acids as in highly aerobic, trained muscle. Consequently, inhibition of triglyceride synthesis may not be a straightforward strategy, either in terms of its achievement pharmacologically or in its anticipated outcomes. The metabolic complexities of triglyceride synthesis, with particular reference to the diacylglycerol acyltransferases (DGATs) are considered in this short review.
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Contents

1. Introduction

Obesity and associated pathologies are increasing in incidence throughout westernised societies. The accumulation of fat (in the form of triglycerides) in adipose tissue is now recognised as not being an innocuous use of this tissue as a 'sink' for the storage of excess body energy intake over expenditure. The changes to whole-body metabolism that accompany even moderate increases in body adiposity are known to result in increased risks of such chronic conditions as type-2 diabetes and cardiovascular disease. Consequently, the synthesis of triglycerides has become a potential target for pharmacological intervention, in the knowledge that it may not only be useful in preventing obesity, but that it is also important in determining the physiology of other cell-types. These include the enterocytes in which triglyceride (re)synthesis is an essential process of dietary fat secretion by the gut,

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and hepatocytes in which failure of triglyceride secretion to match the availability of fatty acids for triglyceride synthesis results in the development of fatty liver, a condition associated with whole-body insulin resistance, and in extreme cases, steatohepatitis. Conversely, over-secretion of triglyceride by the liver is itself an important pharmacological target owing to the close correlation between dyslipidaemia and cardiovascular risk.

In this article the enzymes that have emerged as the molecular targets of such pharmacological strategies will be discussed, with particular emphasis on the possibility that they may be specialised for particular metabolic functions. These are important considerations when devising strategies that may result in enzyme- and/or tissue-specific pharmacological agents.

Triglycerides are the molecules through which long-chain fatty acyl moiety storage and transport occurs in mammals. Other esterified forms of fatty acids exist (e.g. cholesteryl esters) but they do not provide the capacity or versatility of triglycerides in mediating this range of functions. Although the source of the acyl chains can be traced to several different origins, triglyceride molecules can only be synthesised ultimately from diglycerides, in the final reaction of whichever synthetic route is used. This dedicated reaction of triglyceride synthesis is catalysed by enzymes having diacylglycerol acyltransferase (DGAT) activity which resides not only in enzymes that have been specifically designated as such transferases. The activities are ubiquitously distributed (although to very different extents) in many cell-types. However, only very few cell-types are specialised for the synthesis of TG for storage (adipocytes) or (as in hepatocytes and enterocytes) assembly into lipoproteins — the form in which triglycerides are transported between tissues. In other cell-types, triglycerides may accumulate as a local store for the provision of cellular fuel (e.g. cardiomyocytes, Type-1 skeletal muscle fibres), but 'ectopic' (i.e. non-adipose) accumulation of TG is usually indicative of an over supply of fatty acids to a tissue, in excess of what it can oxidise (myocytes) and/or secrete (hepatocytes, enterocytes).

2. Proteins that catalyse triglyceride synthesis from diglycerides

Three genes that encode proteins with substantial DGAT enzyme activity have been described: DGAT1 (Cases et al., 1998) and DGAT2 (Cases et al., 2001; Lardizabal et al., 2001a, 2001b), and monacylglycerol acyltransferse 3 (MGAT 3) which is found in higher mammals, including humans, but not rodents (Cao et al., 2007). DGAT1 belongs to the same family of proteins as the acyl-cholesterol acyltransferases (ACATs), whereas DGAT2 belongs to a different family of proteins to which the MGATs belong (Lardizabal et al., 2001a, 2001b). In mammals, DGAT 1 is expressed in skeletal muscle, skin, intestine (ileum, colon) and testis, with lower levels of expression in liver and adipose tissue (Cases et al., 1998). DGAT 1 appears to be the only one of the two to be expressed in the milk-secreting epithelial cells of the mammary gland (see below). DGAT 2 is similarly widely expressed with high expression levels in hepatocytes and adipocytes (Cases et al., 2001). Both the different tissue-distributions, and the fact that the two major proteins with DGAT activity have been evolved from two completely different protein families indicate that these enzymes have specialised functions even though they catalyse the same reaction.

Neither DGAT1 nor DGAT2 show particular fatty acyl-CoA specificity in vitro. However mice in which the *Dgat 1* gene is disrupted (*Dgat 1*$^{-/-}$) have a lower proportion of 16:1 and more 16:0 and 18:0 fatty acids in their triglycerides (Chen et al., 2002a). As with most enzymes that operate in a membrane micro-environment and catalyse the interconversion of highly hydrophobic molecular species, extrapolation from data obtained in vitro to the situation in vivo is particularly fraught with difficulties. The most experimentally useful kinetic difference between DGATs 1 and 2 is that the activity of the latter is inhibited to a greater extent by concentrations of $MgCl_2$ higher than 10 mM (Cases et al., 2001). Both proteins are expressed in the endoplasmic reticulum. However, their respective over-expression in the hepatoma-derived cell line McA-RH7777 cells (Stone et al., 2004) results in markedly different intracellular patterns of TG droplet accumulation within the cells, suggesting that the intracellular distribution of the two enzymes is different. Thus, over-expression of DGAT 1 results in small TG droplets arranged peripherally within the cells, whereas over-expression of DGAT 2 results in much larger TG droplets disposed more centrally (Stone et al., 2004).

The DGAT and MGAT enzymes can catalyse reactions other than those originally described for them, and can use a wide range of substrates. For example, DGAT 1 appears to be responsible for most of the retinol acyltransferase activity in the retinol esterification pathway, and DGAT 2 (together with MGATs 1 and 2) also has wax-ester synthase activity (see (Orland et al., 2005; Yen et al., 2005).

3. Insights into the functions of different DGAT activities

Insights into the functional importance of DGATs 1 and 2 have been gained from the phenotypes of mice in which the genes of the two enzymes have been knocked-out or over-expressed either globally or in a tissue-specific manner. Such small-animal models are useful in identifying broad principles of function. However, it is to be recognised that it is not always possible to extrapolate from these models to the effects of inhibition of the analogous protein(s) in humans. Nor is it possible to discount the possibility, particularly in global gene knock-out approaches, that what is observed is primarily the result of life-time counter-regulatory responses in the animal model being studied. In this respect the more recent adoption of shorter-term knock-down technologies are likely to be more informative.

Mice in which the DGAT1 gene is globally disrupted throughout life (*Dgat 1*$^{-/-}$) are viable and have a non-remarkable phenotype when maintained on a normal low-fat chow diet, except that females cannot lactate, and the development of the mammary gland is impaired (Cases et al., 2004) indicating that mammary secretory epithelial cells may only express this one protein having DGAT activity (Chen et al., 2002b; Smith et al., 2000). These mice have slightly lower hepatic TG levels when fed a low-fat diet, but on a high-fat diet they have a significantly lowered hepatic TG content (Chen et al., 2002b; Smith et al., 2000). Surprisingly, they have normal plasma fatty acids and their fasting plasma TG levels are not different on either diet. However, they have 50% less adipose tissue in spite of an increased dietary intake. Most importantly, they are more insulin- and leptin-sensitive and are resistant to obesity when fed a high-fat diet. The lean phenotype appears to be achieved through a higher level of physical activity level when the animals are fed a high-fat diet (Smith et al., 2000), although increased thermogenesis also appears to be involved, with increased surface heat loss maintaining a normal core temperature (Chen et al., 2002b). *Dgat 1*$^{-/-}$ mice are able to secrete chylomicron triglycerides from the gut at basal rates, but their capacity for doing so in response to a fat bolus meal is limited (see below). Skin lipid metabolism is also impaired.

DGAT2 is essential for post-natal survival and especially for proper skin function (Stone et al., 2004). Thus, *Dgat 2* $^{-/-}$ mice die soon after birth due to the absence of an efficient wax-ester dependent water-barrier in their skin; they have severe deficiency of TG in their tissues and extreme hypolipidaemia (Stone et al., 2004). Evidently, DGAT1 is unable to compensate for DGAT2 deficiency, underlining the different roles that the two enzymes perform in vivo. In particular, *Dgat2*$^{-/-}$ mice lack essential fatty acids within their acylceramides, suggesting that DGAT2 is specialised for the incorporation of unsaturated fatty acids in triglycerides possibly through its co-localization with desaturase activity and substrate channelling between the two enzymes. In this respect, Ntambi and colleagues (Man et al., 2006) have found that when over-expressed in HeLa cells, DGAT 2 occurs in the same cellular location as stearoyl-CoA desaturase 1 (SCD1) with which it co-immunoprecipitates and interacts closely. Expression of both

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