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Human digestive and metabolic lipases—a brief review

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Abstract

The major human lipases include the gastric, pancreatic and bile-salt-stimulated lipase that aid in the digestion and assimilation of dietary fats, and the hepatic, lipoprotein and endothelial lipase that function in the metabolism of lipoproteins. The triacylglycerol and phopholipase activities of these enzymes enable these varied functions. The lipase enzymes exhibit a high degree of sequence homology not only within but also across species. This and the diverse chromosomal location of their genes point to a multigenic family of enzymes involved in absorption and transport of lipids. Inactivation of lipolytic activity of microorganisms to control infection, inhibition of digestive lipase to control obesity, stimulation of metabolic lipase to reduce hyperlipidemia or procoagulant state, or use of pancreatic lipase supplement in the management of cystic fibrosis are examples of how lipase activity modulation can impact human health.

Keywords: Lipase; Anti-lipase agents; Anti-obesity agents; Fibrates; Heparin

1. Introduction

Lipases are fat-digesting enzymes that include triacylglycerol- and phospholipases. Triacylglycerol lipase catalyzes the hydrolysis of triacylglycerol to free fatty acid, mono- and diacylglycerol. Phospholipase catalyzes the hydrolysis of phospholipids. Phospholipase A catalyzes the hydrolysis of phospholipids to free fatty acid and lysophospholipid; phospholipases A_1 and A_2 attack ester bonds in positions 1 and 2 of the phospholipid respectively. Phospholipase B catalyzes the generation of free fatty acid and glycerylphospholipid, and phospholipase C catalyzes the generation of diacylglycerol and a phosphoryl base. Free fatty acids are utilized for energy production in the muscle or are re-esterified for storage in the adipose tissue [1,2]. The human lipases include the pre-duodenal lingual and gastric lipase and the extra-duodenal pancreatic, hepatic, lipoprotein and the recently described endothelial lipase [3,4]. The aim of this communication is to present a short, basic review of human digestive and metabolic lipases (Fig. 1), and describe the implications of inhibition or stimulation of lipase activity on human health.

2. Pre-duodenal lipase

Gastric lipase (EC 3.1.1.3) is the predominant pre-duodenal lipase in humans; lingual lipase is present in trace amounts. In rodents, lingual lipase is predominant [5]. Gastric lipase is secreted in the gastric juice by the chief cells of fundic mucosa in the stomach. The serous von Ebner glands of the tongue secrete lingual lipase in the saliva [6,7]. Human gastric and rat lingual lipase share a high degree of sequence homology and have identical gene organizations suggesting that rat lingual lipase is the equivalent of human gastric lipase [8]. The gene encoding

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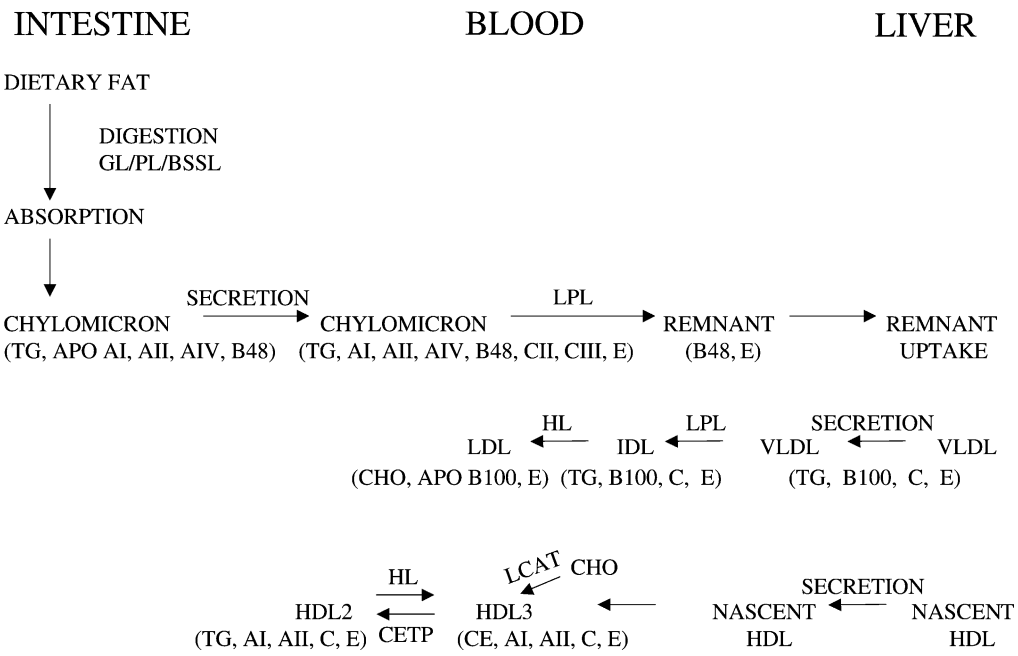

Fig. 1. A schematic outline of lipase function in digestion and transport of lipids. GL: gastric lipase; PL: pancreatic lipase; BSSL: bile-salt-stimulated lipase; LPL: lipoprotein lipase; HL: hepatic lipase; TG: triglyceride; APO: apolipoproteins; CHO: cholesterol; CE: cholesteryl ester; CETP: cholesteryl ester transfer protein; LCAT: lecithin cholesterol acyl transferase.

human gastric lipase has been localized on chromosome 10q23.2 [9,10]. The lingual and gastric lipases have lower molecular weights and greater pH stability than enzymes of the lipase superfamily.

3. Human lipase superfamily

The pancreatic, hepatic, lipoprotein and endothelial lipase are members of the lipase gene family. These enzymes share a high degree of primary sequence homology [11] and similar tertiary structure as suggested by mostly conserved disulfide bonds [12]. The chromosomal localization of the genes encoding these lipases and their tissue of origin has been described (Table 1).

3.1. Pancreatic lipase

Pancreatic lipase (EC 3.1.1.3) produced by the pancreatic acinar cells, is one of the exocrine enzymes of pancreatic juice that is essential for digestion of dietary fats in the intestinal lumen. Hydrolysis of dietary triacylglycerols by both gastric and pancreatic lipase is essential for their absorption by enterocytes, to facilitate assimilation of dietary fat in the body. The substrate of pancreatic lipase is not a single molecule but

Table 1
Human lipase gene family

Lipase	Chromosomal localization of gene	Tissue of origin	References
Pancreatic lipase	10q26.1	Pancreas	[13,14]
Hepatic lipase	15q21–q23	Liver	[15,16]
Lipoprotein lipase	8p22	Adipose, heart, skeletal muscle	[17]
Endothelial lipase	18q21.1	Endothelial cells, liver, lung, kidney, placenta	[18,19]

a non-aqueous phase of aggregated lipids made up of aggregates of ester molecules, micelles or monolayers interfacing with an aqueous medium [20,21]. Pancreatic lipase requires colipase—a pancreatic protein—as cofactor for its enzymatic activity. Colipase relieves phosphatidyl choline-mediated inhibition of the interfacial lipase–substrate complex, helps anchor the lipase to the surface and stabilizes it in the 'open', active conformation [22,23].

Acting together with colipase-dependent pancreatic lipase in the intestinal digestion of dietary lipids is the bile-salt-stimulated lipase, which is a component of pancreatic juice and human milk. While colipase-dependent pancreatic lipase facilitates the uptake of fatty acids, bile-salt-stimulated lipase facilitates the uptake of free cholesterol from the intestinal lumen [24]. Recent experimental evidence suggests that bile-salt-stimulated lipase binds avidly to heparin unlike colipase-dependent pancreatic lipase, which contradicts the earlier opinion of a common intestinal heparin-like receptor for both these enzymes [25].

3.2. Lipoprotein lipase

Lipoprotein lipase (EC 3.1.1.34) is a non-covalent homodimeric protein produced mainly by the adipose, heart and muscle tissue and to some extent by macrophages [26,27]. The functional site of the active enzyme is the luminal surface of the capillary endothelium of the tissue of origin where it is bound to glycosaminoglycan structures [26], presumably indirectly through another protein [28]. Lipoprotein lipase catalyzes the hydrolysis of triacylglycerol present in very low-density lipoprotein (VLDL) and chylomicron particles to generate triglyceride-poor intermediate-density lipoprotein (IDL) and chylomicron remnants, respectively. Apolipoprotein CII (Apo CII) present on VLDL particles is the co-factor required for activating the enzyme [29]. The enzyme is released in circulation from its endothelial-binding site upon injection of heparin [29]. Lipoprotein lipase has multiple functional domains such as the lipid-binding domain where interaction of the enzyme with the lipoprotein substrate takes place. This results in a conformational change that leads to the movement of a short helical segment or 'lid' to expose the active site containing the Ser-Asp-His catalytic triad, where hydrolysis of triacylglycerol takes place [30,31]. This catalytic triad characteristic also of serine proteinases, is common for lipase enzymes across species. The other functional domains of lipoprotein lipase include the dimer formation, heparin binding, cofactor interaction and fatty acid-binding domains [30–32]. Post-translational phosphorylation via the cyclic AMP pathway regulated by hormones converts the enzyme to its active from [33].

3.3. Hepatic lipase

Hepatic lipase (EC 3.1.1.3) as the name suggests, is produced by hepatocytes in the liver. In rats, the enzyme is also present in the adrenals and ovaries [34]. Like lipoprotein lipase, hepatic lipase also binds to endothelial cells but only within the liver from where it is released upon injection of heparin. Unlike pancreatic or lipoprotein lipase, hepatic lipase does not require a cofactor for its activity, is stable at high salt concentrations and is inactivated by sodium dodecyl sulfate, properties that are used to differentiate between hepatic and lipoprotein lipase in non-immunological assay of enzyme activity in post-heparin plasma [35,36]. The preferred physiological substrate of hepatic lipase is triglyceride of IDL particle, which it hydrolyses to form triglyceride-poor and cholesterol-rich low-density lipoprotein (LDL). Hepatic lipase also converts post-prandial triglyceride rich high-density lipoprotein (HDL) particle (i.e. HDL_2) to post-absorptive triglyceride poor HDL (i.e. HDL_3) [37].

Several mutations in the genes encoding human lipoprotein and hepatic lipase affect their activity [38]. A common substitution in exon 6 of lipoprotein lipase gene (Asn291Ser) was associated with reduced HDL-cholesterol levels and increased risk of coronary heart disease [39,40]. In case of hepatic lipase gene, a C-to-T transition at position −514 in the promoter region was shown to be associated with raised levels of HDL-cholesterol [41].

3.4. Endothelial lipase

Endothelial lipase (EC 3.1.1.3) is a recent addition to the lipase gene family [4]. It has 45% primary sequence homology with lipoprotein lipase, 40% with hepatic lipase and 27% with pancreatic lipase. Unlike lipoprotein or hepatic lipase, endothelial lipase

is produced by the endothelium. Other tissues expressing this enzyme include lung, liver, kidney and placenta. Heart and skeletal muscles, which express large amounts of lipoprotein lipase, do not express endothelial lipase [19]. Endothelial lipase differs from the other enzymes of the lipase gene family in the sequence of the 'lid' domain that forms an amphipathic helix covering the catalytic site of the enzyme as already described. Its 19-residue 'lid' region is 3 residues shorter and less amphipathic than 'lid' region of lipoprotein or hepatic lipase [19]. This indicates a different enzymatic function. Indeed, unlike lipoprotein or hepatic lipase that have triacylglycerol lipase activity, endothelial lipase has primarily a phospholipase A_1 activity. This is evident from the triacylglycerol lipase to phospholipase activity ratio of 0.65 for endothelial lipase, compared with 24.1 for hepatic and 139.9 for lipoprotein lipase. Like hepatic and unlike lipoprotein lipase, endothelial lipase does not require apolipoprotein CII for activation. Like lipoprotein but not hepatic lipase, the triacylglycerol and phospholipase activities of endothelial lipase are inhibited by 1 M sodium chloride [42]. Overexpression of endothelial lipase in mice resulted in reduced HDL-cholesterol and apolipoprotein A_1 levels, and its deficiency led to increased HDL-cholesterol levels suggesting that it plays a physiologic role in HDL metabolism probably by catalyzing hydrolysis of HDL phospholipids thereby facilitating a direct HDL receptor-mediated uptake. Endothelial lipase may also facilitate the uptake of apolipoprotein B-containing remnant lipoprotein. As the placental tissue abundantly expresses endothelial lipase, it may also have a role in the development of fetus [4,19].

4. Therapeutic use of digestive (pancreatic) lipase preparations

Most of the patients with cystic fibrosis require daily pancreatic enzyme supplements containing lipase, amylase and protease, to relieve the symptoms of exocrine pancreatic insufficiency. Pancreatic enzyme supplementation is also useful in the management of patients with celiac disease—a condition affecting the intestinal tract and causing nutrient malabsorption, or in Crohn's disease, which may be associated with a deficiency of pancreatic enzymes [43]. Lipase and other pancreatic enzyme supplements are available in tablet or capsule forms. High dose of pancreatic enzyme supplement was found to be associated with fibrosing colonopathy in children with cystic fibrosis, and a daily dose of less than 10,000 units lipase activity/kg body weight was recommended [44]. The use of pancreatic enzyme supplements is understandably contraindicated in those on medication with lipase inhibitors.

5. Inhibition of lipase activity—control of infection and management of obesity

5.1. Anti-microbial action

Extracellular lipolytic activity enables certain microbial pathogens to grow on skin and mucosal linings by using lipids present on these surfaces as the source of carbon. An important example is the human pathogen *Candida albicans*, which not only infects the skin and mucosa but can also cause severe systemic infection. Besides a certain degree of host immunosuppression, the multiple gene-controlled expression and secretion of lipase and aspartate proteinase by *Candida* spp. determine the stage of infection and virulence [45,46]. Inhibitors of microbial lipase conceivably have the potential to control infections caused by lipase secreting microorganisms, and hence the relevance of development of anti-microbial lipase agents. In this context, natural products such as berberine, sanguinarine and related alkaloids were found to possess anti-lipase activity against *C. rugosa* lipase [47].

5.2. Anti-obesity agents

Obesity poses a significant health problem in today's world. It is a risk factor for clinical disorders such as hypertension, hyperlipidemia, diabetes mellitus and cardiovascular disease. Although reduction of caloric intake by diet and increased level of physical activity are well-known approaches for achieving weight loss, the need for drugs to supplement diet and exercise is fast gaining acceptance. Anti-obesity drugs may act by: (i) reducing food intake, (ii) altering metabolism, or (iii) increasing thermogenesis [48]. Anti-lipase agents are inhibitors of digestive lipases such as gastric and pancreatic lipase. As hydrolysis

of dietary triacylglycerol is essential for subsequent absorption by enterocytes, anti-lipase agents function by reducing or blocking the availability of dietary fat calories by preventing assimilation of fats, and thus mimic the effect of reduced food intake. One of the first potent inhibitors of pancreatic lipase to be described was lipstatin, isolated from *Streptomyces toxytricini*. The beta lactone structure of lipstatin was shown to cause inhibition of pancreatic lipase at a 50% inhibitory concentration of 0.14 μM [49]. Tetrahydrolipstatin (Orlistat®), a synthetic analogue of lipstatin, was later developed and is currently in clinical use for the treatment of obesity [50,51]. Other promising synthetic lipase inhibitors under investigation include 2-oxo amide triacylglycerol analogues [52] and long chain α-keto amide derivatives [53]. Besides the synthetic chemical compounds, an extract from the herb *Nomame herba* was recently reported to inhibit porcine pancreatic lipase in vitro, and to reduce gain of body weight and triglyceride elevation without affecting food intake in lean rats fed on a high fat diet [54]. A physiological peptide that reduces fat intake, bodyweight and body fat is enterostatin formed by cleavage of pancreatic procolipase. Obese persons secreted less pancreatic procolipase than non-obese persons. The release of enterostatin in the gastrointestinal lumen is induced by high fat diet. Its anorectic effect is the result of its action on the central and peripheral nervous system, leading to multiple metabolic effects including reduced insulin and increased adrenal corticosteroid secretion, and enhanced sympathetic drive to brown adipose tissue [55].

6. Stimulation of lipase activity

Hyperlipidemia or high levels of serum triglyceride and cholesterol, as in Fredrickson Type IIb, III or IV hyperlipidemia is a risk factor for premature atherosclerosis [56,57]. Hypertriglyceridemia may result from decreased removal of circulating triglyceride due to decreased activity of lipoprotein lipase, or from increased hepatic secretion of triglyceride-rich VLDL. In either case, stimulation of lipoprotein lipase activity would be expected to lower the triglyceride levels by catalyzing its hydrolysis. One of the mechanisms of action of the fibrate group of drugs considered to be most effective in lowering serum triglyceride levels [58], is enhancement of lipoprotein lipase activity [59–61]. Moreover, fibrates bring about increased uptake and oxidation of fatty acids in the muscle [60], decreased synthesis and secretion of VLDL by the liver and increased synthesis of apolipoprotein A_1 [62], and down regulation of apolipoprotein CIII gene expression [63]. Apo CIII is an inhibitor of Apo CII-mediated activation of lipoprotein lipase activity. Besides fibrates, a statin drug namely simvastatin—an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase enzyme, was recently reported to also increase glycerol ester hydrolase (lipase) activity in the serum of men with coronary heart disease [64]. Thus, drug-induced stimulation of lipase activity is relevant in the management of hyperlipidemia particularly hypertriglyceridemia.

Besides fibrates or statins, another triglyceride-lowering substance is the anti-coagulant, heparin. The lipolytic effect of heparin is mediated by the release in circulation of lipoprotein and hepatic lipase from their endothelial binding sites [29]. Raised levels of these enzymes and concomitant lowering of triglyceride can be demonstrated in post-heparin plasma [35]. Apart from lipases, heparin also mediates the release of full-length tissue factor pathway inhibitor (TFPI)—a Kunitz-type coagulation protease inhibitor, into circulation from its endothelial-binding site. TFPI functions as a natural anti-coagulant by forming a quaternary complex with tissue factor and activated factor VII complex, and factor X. The quaternary complex so formed blocks further activation of factor X, and limits the generation of thrombin [65].

A positively charged synthetic peptide of the C-terminal region of full-length TFPI and the full-length TFPI itself stimulated the activity of bovine lipoprotein lipase in vitro, unlike TFPI truncated at the C-terminus. Incubation of post-heparin plasma (containing lipoprotein and hepatic lipase and, full-length TFPI) with antibody against the C-terminal region of TFPI inhibited the enzymatic activity of lipoprotein lipase [66]. These observations suggest that the positively charged domain of full-length TFPI sequesters the negatively charged fatty acid product of lipase catalysis thus relieving the known product inhibition of lipase activity and driving the enzymatic reaction forward, thereby registering enhancement of the enzymatic activity. The presumed physiological

significance is enhanced hydrolysis of plasma triglyceride with concomitant inhibition of factor VII coagulant activity [35,67] to limit the generation of thrombin as demonstrated in vitro by prolonged plasma clotting time in the presence of C-terminal peptide of TFPI [68]. Although heparin preparations are not used in clinical practice to lower triglyceride levels, their administration nonetheless brings about lowering of triglyceride and factor VII coagulant activity in vitro and in vivo [35,67].

In conclusion, inhibition of microbial lipase activity to control infection or that of digestive lipase activity to control obesity, stimulation of lipase activity to reduce hyperlipidemia or a procoagulant state, or administration of lipase enzyme as supplement in the management of clinical disorders such as cystic fibrosis or Crohn's disease, are all relevant to human health.

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