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Phospholipase A₂ enzymes in metabolic and cardiovascular diseases

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Abstract

Purpose of review—The phospholipase A₂ (PLA₂) family of proteins includes lipolytic enzymes that liberate the *sn*-2 fatty acyl chains from phospholipids to yield non-esterified fatty acids and lysophospholipids. The purpose of this review is to discuss recent findings showing distinct roles of several of these PLA₂ enzymes in inflammatory metabolic diseases such as diabetes and atherosclerosis.

Recent findings—The Group 1B PLA₂ (PLA₂G1B) digestion of phospholipids in the intestinal lumen facilitates postprandial lysophospholipid absorption, which suppresses hepatic fatty acid oxidation leading to increased VLDL synthesis, decreased glucose tolerance, and promotion of tissue lipid deposition to accentuate diet-induced obesity, diabetes, and hyperlipidemia. Other secretory PLA₂s promote inflammatory metabolic diseases by generating bioactive lipid metabolites to induce inflammatory cytokine production, whereas the major intracellular PLA₂s, cPLA₂α and iPLA₂, generate arachidonic acid and lysophosphatic acid in response to extracellular stimuli to stimulate leukocyte chemotactic response.

Summary—Each member of the phospholipase A₂ family of enzymes serves a distinct role in generating active lipid metabolites that promote inflammatory metabolic diseases including atherosclerosis, hyperlipidemia, obesity, and diabetes. The development of specific drugs that target one or more of these PLA₂ enzymes may be novel strategies for treatment of these chronic inflammatory metabolic disorders.

Keywords

Obesity; diabetes; hyperlipidemia; atherosclerosis; inflammation; lysophospholipid

Introduction

The phospholipase A₂ (PLA₂) family of proteins includes lipolytic enzymes that catalyze the hydrolysis of the ester bond at the *sn*-2 position of phospholipids to yield free fatty acids and

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Conflicts of interest

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lysophospholipids. Currently, these enzymes are classified into 5 major groups with many subgroups depending on their functions and cellular locations. The secreted PLA₂ enzymes are small secreted proteins of 14–18 kDa. The lipoprotein-associated PLA₂ is also a secreted enzyme but it has platelet-activating factor acetylhydrolase activity and is associated with plasma lipoproteins. The other 3 groups of PLA₂ enzymes are located intracellularly: the cytosolic PLA₂s (molecular sizes of 61–114 kDa) that are calcium-dependent, the calcium-independent PLA₂s (85 to 88-kDa) that are also present in the cytosol, and the lysosomal PLA₂ that functions exclusively in the lysosomes with optimal activity at lower pH. Research over the past decade using genetically-modified mouse models and association studies in humans have indicated distinct roles of each PLA₂ in biological processes such as digestion, tissue injury/repair, host defense, inflammation, atherosclerosis, and obesity/diabetes. This review will focus primarily on the recently discovered role of the group 1B phospholipase A₂ (PLA2G1B) in obesity/diabetes, hyperlipidemia, and atherosclerosis. The influence of other PLA₂s in these metabolic disorders will be discussed briefly for comparison. Readers interested in these PLA₂ enzymes are referred to several excellent recent review articles for more details [1–4].

Group 1B Phospholipase A₂

The PLA2G1B is a secreted phospholipase expressed primarily in the acinar cells of the pancreas and to lesser extent also in the lung and islet β -cells. In pancreatic acinar cells, PLA2G1B is found within zymogen granules along with other digestive enzymes. Upon meal feeding, contents within the zymogen granules are released into pancreatic juice and transported to the intestinal lumen where the enzymes can mediate nutrient digestion and absorption. Based on its enzymatic activity in hydrolyzing phospholipids, the role of PLA2G1B in the digestive tract was presumed to be the hydrolysis of phospholipids, thereby contributing to the necessary remodeling of lipid particles in the intestinal lumen prior to lipid nutrient absorption. However, knockout mouse studies revealed that PLA2G1B is not the only phospholipid hydrolytic enzyme in the digestive tract, and other phospholipases in the intestine can compensate for the lack of this enzyme in catalyzing phospholipid digestion and intestinal lipid absorption in *Pla2g1b*-null mice.

Genome-wide association studies have identified polymorphisms in the *PLA2G1B* gene as a determinant of central obesity in humans [5]. The association between *PLA2G1B* gene polymorphism and obesity in humans can be recapitulated in genetically-modified mouse models, with *Pla2g1b*-null mice displaying resistance to diet-induced obesity, hyperglycemia, and hyperinsulinemia whereas transgenic over-expression of the *Pla2g1b* gene in pancreas accentuates these metabolic diseases [6, 7]. The differences in sensitivity to diet-induced metabolic diseases between wild type *Pla2g1b*^{+/+} mice with *Pla2g1b*^{-/-} and *Pla2g1b*-transgenic mice are not due to differences in food intake. Although the most straight forward explanation for their metabolic differences is that PLA2G1B may be required for complete phospholipid hydrolysis when lipid input into the intestinal lumen exceeds the capacity of the compensatory mechanism, similar amount of fat was found to be absorbed between these animals when they were fed the high fat diet. Additionally, the fat-fed *Pla2g1b*^{-/-} mice absorbed more fat than chow-fed *Pla2g1b*^{+/+} mice yet their body weight gains were similar [6]. The *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice also displayed similar fat

absorption efficiency when maintained on a low-fat chow diet, yet the *Pla2g1b*^{-/-} mice displayed increased glucose tolerance and insulin sensitivity compared to their wild type counterparts under these conditions [6]. These results indicated that PLA2G1B has a direct role in regulating adiposity, glucose metabolism, and insulin sensitivity, and this unique property of PLA2G1B is not shared by other phospholipases in the intestinal tract.

One difference in intestinal phospholipid digestion between *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice is the lipolytic products formed and absorbed after meal consumption. The *Pla2g1b*^{+/+} mice absorbed significantly more lysophospholipids into the liver and circulation compared with *Pla2g1b*^{-/-} mice, but the absorption of phospholipid-derived fatty acids and phosphatidylcholine-associated choline was found to be similar between *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice [8]. These results suggested that the compensatory enzyme for phospholipid digestion in the intestinal lumen in the absence of PLA2G1B is not specific for the ester bond at the *sn*-2 position of phospholipids, but can release both *sn*-1 and *sn*-2 fatty acyl chains from phospholipids to yield 2 nonesterified fatty acids and glycerophosphocholine for absorption by enterocytes. In contrast, luminal digestion of diet- and/or biliary-derived phospholipids by PLA2G1B yields nonesterified fatty acids and lysophospholipids that can be rapidly absorbed by intestinal cells.

Differences in lysophospholipid absorption accounted for the differences between *Pla2g1b*^{+/+}, *Pla2g1b*^{-/-}, and *Pla2g1b*-transgenic mice in their sensitivity to diet-induced metabolic diseases. Postprandial lysophospholipid levels were significantly lower in *Pla2g1b*^{-/-} mice and higher in *Pla2g1b*-transgenic mice compared to those observed in wild type *Pla2g1b*^{+/+} mice. The infusion of lysophospholipids into *Pla2g1b*^{-/-} mice to levels similar to the levels observed during the postprandial state of *Pla2g1b*^{+/+} mice abolished the protective effects of *Pla2g1b* gene deletion against exaggerated postprandial insulin resistance and hyperglycemia [8]. Lysophospholipids promote postprandial hyperglycemia by reducing glucose uptake by the liver, heart, and muscle tissues, as well as suppressing insulin-stimulated glycogen synthesis in the liver [8]. Lysophospholipids administration also ameliorated the enhanced hepatic fatty acid oxidation observed in *Pla2g1b*^{-/-} mice, thereby increasing substrate availability for deposition into adipose tissues to promote obesity [9]. Lysophospholipids reduce fatty acid oxidation by inhibiting the expression of peroxisome proliferator-activated receptor (PPAR)- α , - δ , and - γ genes as well as genes for proteins responsible for fatty acid transport and utilization such as CD36 and UCP2 [9].

The reduced hepatic fatty acid oxidation due to PLA2G1B-mediated lysophospholipid absorption also increases fatty acid substrates available for triglyceride biosynthesis [10]. Additionally, lysophospholipids are also efficiently re-acylated to phospholipids as well as promote triglyceride synthesis [11]. Lysophospholipids also prevent premature intracellular degradation of apoB in the liver [12]. Therefore, PLA2G1B-mediated lysophospholipid absorption promotes hyperlipidemia by accentuating hepatic VLDL synthesis and secretion after fat feeding [10]. Moreover, *PLA2G1B* gene inactivation has also been reported to improve plasma clearance of triglyceride-rich lipoproteins in high fat-fed mice [10], suggesting that lysophospholipids derived from PLA2G1B-mediated phospholipid hydrolysis in the digestive tract may also suppress the expression of LDL receptor and/or LDL receptor-related proteins in the liver. Taken together, these results indicate that the

underlying mechanism by which *PLA2G1B* gene inactivation protects against diet-induced hyperlipidemia is also mediated via reducing lysophospholipid absorption after fat feeding, thereby ameliorating diet-induced postprandial VLDL synthesis and increasing plasma clearance of triglyceride-rich lipoproteins. The lower plasma lipid levels in *Pla2g1b*^{-/-} mice are likely to reduce lipid deposition to adipose tissues, skeletal muscle, and the vessel wall, thereby may also indirectly suppress diet-induced obesity, insulin resistance, and atherosclerosis through this mechanism. A schematic diagram depicting the model of how PLA2G1B influences lipid metabolism and related metabolic diseases is shown in Figure 1.

The resistance of *Pla2g1b* gene inactivated mice to diet-induced obesity, diabetes, and hyperlipidemia suggests that the PLA2G1B protein may be a novel therapeutic target for treatment of these metabolic disorders. This possibility has been explored in a pre-clinical model testing the efficacy of the PLA2G1B inhibitor methyl indoxam to suppress body weight gain and hyperglycemia in response to a high fat/high carbohydrate diet in mice. When mixed with food and administered orally, methyl indoxam did not alter food intake or lipid nutrient absorption but significantly reduced postprandial lysophospholipid levels in a concentration-dependent manner, indicating the suppression of PLA2G1B activity *in vivo* [13]. Importantly, oral methyl indoxam administration reduced high fat/high carbohydrate diet-induced body weight gain in a dose-dependent manner [13]. Fasting blood glucose levels and glucose tolerance in high fat/high carbohydrate-fed mice were also dramatically improved with methyl indoxam treatment, to levels similar to those observed in mice fed a low-fat control diet [13]. Oral methyl indoxam administration had no effect on body weight and blood glucose levels in chow-fed animals, thus indicating that the reduced body weight gain and improved glucose tolerance with methyl indoxam treatment were not due to adverse effects but a direct consequence of suppressing PLA2G1B activity *in vivo*. Finally, whereas 10 weeks of feeding the high fat/high carbohydrate diet increased fasting plasma cholesterol levels in wild type C57BL/6 mice, the inclusion of methyl indoxam in the high fat/high carbohydrate meal suppressed diet-induced hypercholesterolemia, reducing plasma cholesterol levels to levels observed in chow-fed wild type mice or in *Pla2g1b*^{-/-} mice fed either chow or high fat/high carbohydrate diet (Figure 2).

The effectiveness of oral methyl indoxam administration to reduce diet-induced obesity, hyperglycemia, and hypercholesterolemia in mice is consistent with the possibility that PLA2G1B inhibition may be a potentially effective oral therapeutic option for treatment of metabolic diseases. However, it is important to note that *in vitro* experiments have documented that methyl indoxam is a general inhibitor capable of inhibiting the activities of other secretory phospholipase A₂ enzymes in addition to PLA2G1B [14]. Although cell culture studies failed to detect methyl indoxam transport from the apical to the basolateral side of intestinal cells [13, 15], thus suggesting that methyl indoxam protection against diet-induced metabolic diseases through direct inhibition of PLA2G1B in the intestinal lumen, *in vivo* measurements revealed limited but significant bioavailability of orally fed methyl indoxam [13]. Whether a non-absorbable PLA2G1B inhibitor, which presumably would be more advantageous with potentially less systemic side effects, can be an effective option, or if inhibition of other phospholipase A₂ enzymes in addition to PLA2G1B inhibition is

necessary to reduce diet-induced obesity, diabetes, and hypercholesterolemia remains to be determined.

Lipoprotein-Associated Phospholipase A₂

The lipoprotein-associated PLA₂ (Lp-PLA₂) is also a secreted protein and is made by lymphocytes, macrophages and mast cells. In addition to the hydrolysis of phospholipids, Lp-PLA₂ is also capable of degrading biologically active oxidized phospholipids (oxPLs) and platelet activating factor. Studies exploring the role of Lp-PLA₂ in metabolic diseases have focused primarily on atherosclerosis. Nevertheless, the role of Lp-PLA₂ in atherosclerosis has not been resolved completely. The hydrolysis of oxPLs by Lp-PLA₂ generates lysophospholipids and oxidized fatty acids, which are pro-inflammation and promote atherosclerosis. The oxPLs have also been reported to have anti-inflammatory properties and function in a negative feedback manner to blunt macrophage inflammatory response [16]. These observations suggest that Lp-PLA₂ is pro-atherogenic by increasing inflammatory response as well as reducing the ability to temper inflammation in response to vascular insults. Surprisingly, adenovirus-mediated transfer of the Lp-PLA₂ gene suppressed injury-induced neointimal hyperplasia and reduced spontaneous atherosclerosis in *apoE*^{-/-} mice [17], suggesting that Lp-PLA₂ is atheroprotective in mice. However, a recent study reported that pharmacological inhibition of Lp-PLA₂ activity also ameliorated inflammation and atherosclerotic plaque formation in *apoE*^{-/-} mice [18]. The differences between these two studies have not been resolved. Thus, the role of Lp-PLA₂ in atherosclerosis development in mice remains unclear. Mallat and colleagues suggested that the role of Lp-PLA₂ in atherosclerosis may be different between humans and mice because the enzyme is associated with HDL in mice and with LDL in humans [1]. In humans, high Lp-PLA₂ levels and activities are associated with coronary heart disease and inflammation [19]. Reducing circulating Lp-PLA₂ levels in patients with acute coronary syndrome was associated with plaque regression [20]. Plasma Lp-PLA₂ levels are also associated with high waist-hip ratio, plasma triglyceride- and LDL-cholesterol levels, and Lp-PLA₂ levels are higher in subjects with metabolic syndrome than in normal subjects [21]. Taken together, these results indicate that Lp-PLA₂ promotes metabolic diseases in humans, suggesting that Lp-PLA₂ may also be a target for intervention. Pre-clinical and clinical testing of efficacy of the Lp-PLA₂-specific inhibitor darapladib in reducing cardiovascular and metabolic diseases are currently underway [22–24].

Other Secreted Phospholipase A₂ Enzymes

Other secreted PLA₂s are similar to PLA2G1B and Lp-PLA₂ in the production of pro-inflammatory mediators such as non-esterified fatty acids and lysophospholipids. The group IIa PLA_s (PLA2G2A) is the most abundant phospholipase A₂ enzyme in human serum. The most commonly used mouse strain for study cardiovascular and metabolic diseases, C57BL/6 mouse is a natural mutant of PLA2G2A. Over-expression of the human *PLA2G2A* gene increases atherosclerosis in wild type and LDL receptor-deficient C57BL/6 mice [25, 26], indicating that PLA2G2A is pro-atherogenic. This enzyme accelerates atherosclerosis through multiple mechanisms including: (i) the hydrolysis of LDL-associated phospholipids to promote remodeling of LDL to smaller and denser LDL particles with increased retention

to matrix proteoglycans at the vessel wall [27], (ii) induction of LDL oxidation and cellular oxidative stress [28], and (iii) direct binding to sPLA₂ receptors on cell surfaces to promote inflammatory cytokine secretion [29]. In the vessel wall, PLA₂G2A can be localized to atherosclerotic lesion areas but the enzyme is not present in normal arteries [30]. The expression of PLA₂G2A by vascular smooth muscle cells is induced during inflammation [31, 32]. Tissue inflammation also elevates PLA₂G2A expression in adipose tissues [32], suggesting that PLA₂G2A not only contributes to atherosclerosis but may also be a contributing factor in other inflammatory metabolic diseases such as diabetes. The potential of sPLA₂ inhibitors for treatment of both of these metabolic disorders has been suggested in a recent review article [23].

Intracellular Phospholipase A₂ Enzymes

The two most prominent intracellular PLA₂ enzymes are the calcium-dependent cPLA₂α (PLA₂G4A) and the calcium-independent iPLA₂ (PLA₂G6). Both enzymes are important inflammatory mediators, responding to extracellular signaling to provide distinct lipid mediators at different intracellular sites that are required for leukocyte chemotaxis [4]. The cPLA₂α enzyme is selective for liberating *sn*-2 arachidonic acids from phospholipids, thereby is essential for signal-activated generation of arachidonic acid-derived lipid metabolites during cell activation. In contrast, iPLA₂ lacks acyl chain specificity but prefers phosphatidic acid instead of phospholipid substrates. Both cPLA₂α-generated arachidonic acid and iPLA₂-mediated lysophosphatic acid production are required for monocyte chemotaxis to monocyte chemoattractant protein-1. Thus, activation of these intracellular PLA₂s by extracellular stimulation is also pro-inflammatory, and potentially contributory to both atherosclerosis and diabetes. Although these results suggest intracellular PLA₂ inhibition may be another approach for treatment of these inflammatory metabolic diseases, a recent report showing cPLA₂ inhibition increases CD36 expression and foam cell formation in a macrophage cell line raises caution to this strategy [33].

Conclusion

Depending on the anatomic site of expression, each member of the phospholipase A₂ family of enzymes serves a distinct role in normal physiology in response to meal consumption and infection, but also generates active lipid metabolites that promote inflammatory metabolic diseases including atherosclerosis, hyperlipidemia, obesity, and diabetes. The PLA₂G1B is expressed primarily in the pancreatic acinar cells and participates in remodeling of dietary lipids in the intestinal lumen prior to lipid nutrient absorption. However, PLA₂G1B elevates lysopholipid levels postprandially leading to increase susceptibility of obesity, diabetes, and hyperlipidemia. The other secretory PLA₂s generates active lipid metabolites that promote oxidative stress and inflammatory cytokine production, whereas the major intracellular PLA₂ enzymes cPLA₂α and iPLA₂ are activated in response to extracellular stimuli in relaying signals for leukocyte chemotactic responses in accentuating inflammatory metabolic diseases. The development of specific drugs that target one or more of these PLA₂ enzymes should be considered as novel strategies to treat chronic inflammatory metabolic diseases such as diabetes and atherosclerosis.

Acknowledgments

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Key Points

- The group 1B PLA₂ (PLA2G1B) promotes lysophospholipid absorption, which suppresses hepatic fatty acid oxidation and leading to promotion of obesity, diabetes, and hyperlipidemia.
- Unique role of each phospholipase A₂ in generating bioactive lipid metabolites that promote inflammation and inflammatory metabolic diseases.
- Pharmacological inhibition of PLA₂ enzyme activities are effective strategies to reduce diet-induced obesity, diabetes, hyperlipidemia, and atherosclerosis.

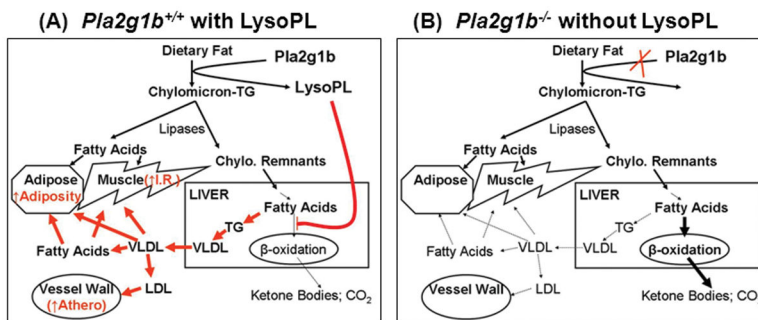


Figure 1. Schematic diagram depicting pathway underlying group 1B phospholipase A₂ inhibition of fatty acid oxidation and promotion of metabolic diseases

Panel A shows pathway in wild type *Pla2g1b*^{+/+} mice, where Pla2g1b-catalyzed hydrolysis of dietary fat and phospholipids generates lysophospholipids (LysoPL) that inhibits fatty acid oxidation in the liver. The increased fatty acid availability in the liver promotes triglyceride (TG) synthesis, leading to elevated VLDL secretion into the plasma circulation. Fatty acids generated directly from lipase-catalyzed hydrolysis of chylomicron-TG as well as from VLDL hydrolysis are deposited in adipose tissues to promote adiposity as well as transported to skeletal muscle to promote insulin resistance (I.R.). The LDL generated from increased lipoprotein secretion can also be accumulating in the vessel wall to promote atherosclerosis. *Panel B* shows pathway in *Pla2g1b*^{-/-} mice, where reduced LysoPL absorption due to Pla2g1b inactivation results in increased hepatic fatty acid oxidation (bold arrow) and reduced TG synthesis and VLDL secretion, ultimately leading to reduced fatty acid deposition in adipose tissue and skeletal muscle and decreased LDL accumulation in the vessel wall.

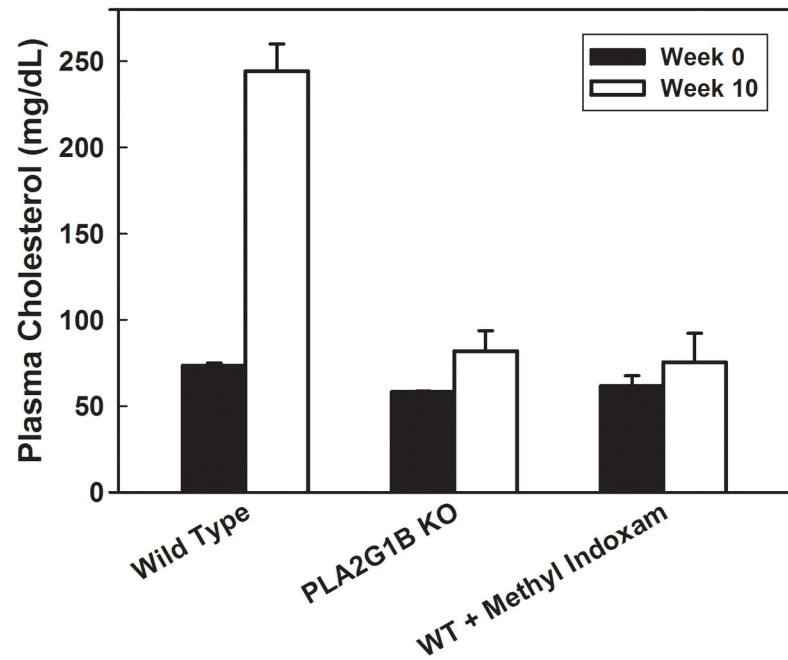


Figure 2. PLA2G1B inactivation protects against diet-induced hypercholesterolemia
Fasting plasma cholesterol levels were measured from wild type (WT) *Pla2g1b*^{+/+} mice and *Pla2g1b*^{-/-} (PLA2G1B KO) mice before (solid bars) and 10 weeks after feeding a high fat/high carbohydrate diet (open bars). Results showed elevation of plasma cholesterol levels in wild type mice after high fat/high carbohydrate feeding, and the diet-induced hypercholesterolemia was not observed in WT mice when PLA2G1B activity was inhibited with oral methyl indoxam administration or in mice with *Pla2g1b* gene inactivation.