Journal of
Obesity & Weight Loss Therapy

Kusunoki et al., J Obes Weight Loss Ther 2013, 3:4
DOI: 10.4172/2165-7904.1000177

Review Article Open Access

Lipoprotein Lipase Activation Improves the Cachexia and Obesity

Masataka Kusunoki[1]*, Kazuhiko Tsutsumi[2], Chen Tana[3], Daisuke Sato[4] and Takao Nakamura[4]

[1]*Department of Internal Medicine, Medical Clinic, Aichi Medical University, Nagoya, Japan*
[2]*Okinaka Memorial Institute for Medical Research, Tokyo, Japan*
[3]*Department of Sports Medicine, Graduate School of Medicine, Nagoya University, Nagoya, Japan*
[4]*Department of Biomedical Information Engineering, Graduate School of Medical Science, Yamagata University, Yamagata, Japan*

Abstract

Cachexia is defined as an extreme wasting condition with marked weight loss. It is observed in paints with cancer and severe infectious disease. Obesity is one of the fasted growing major diseases in developed and developing countries. As has been persuasively argued, long-term imbalance between intake and expenditure of fat is a central factor in the etiology of obesity. We hypothesized that elevating lipoprotein lipase (LPL) activity would cause an improvement of cahexia and obesity. To test this hypothesis, we studied the effects of the LPL activator NO-1886 in cachexia and obese animals.

Keywords: Lipoprotein lipase; Insulin resistance; Lipid metabolism; Obesity; Weight loss

Introduction

Cachexia is defined as an extreme wasting condition with marked weight loss, anorexia, and lassitude [1]. About half of all cancer patients show a syndrome of cachexia characterized by loss of adipose tissue and skeletal muscle mass. Such patients have a decreased survival time compared with that of patients without weight loss [2]. Abnormal metabolism is thought to be the basis of the cachexia status in advanced cancer patients. Cachexia induces the cytokines, in particular tumor necrosis factor (TNF)-α, IL-1, and IL-6 [3-9], is thought to inhibit the activity of lipoprotein lipase (LPL), and thereby induces weight loss as a result of reduced fat accumulation in the tissues. Therefore, it is thought that emaciation of cancer patients might be prevented and cachexia improved by increasing LPL activity.

On the other hand, obesity in adulthood is characterized by adipocyte hypertrophy. Adipose tissue participates in the regulation of energy homeostasis. High-fat diet-induced insulin resistance associated with obesity is a major risk factor for diabetes and cardiovascular disease. Adipose tissue itself serves as the site of triglyceride (TG) storage and free fatty acid release in response to changing energy demands [10].

LPL plays a pivotal role in lipids and the metabolism of lipoprotein [11]. Major functions of LPL include the hydrolysis of TG-rich lipoproteins and release of non-esterified fatty acid (NEFA), which are taken up and used for metabolic energy in peripheral tissue such as muscle, or are re-esterified into TG and stored in adipose tissue. The balance between these competing effects could determine whether increased LPL activity will lead to a reduced rate of weight gain or to increased adiposity through increased rates of adipose tissue storage of TG. An imbalance of LPL activity may alter the partitions of plasma TG between muscle and adipose tissue, and thus influence insulin resistance and obesity.

Institute of Otsuka Pharmaceutical Factory, Inc. synthesized the LPL activator NO-1886 ([4-(4-bromo-2-cyano-phenylcarbamoyl)-benzyl]-phosphonic acid diethyl ester, CAS133208-93-2, generic name: ibrolipim).

Hara et al. reported that LPL activator NO-1886 treatment in high-fructose diet induced insulin resistance rats decreases the respiratory quotient (RQ) and plasma TG [12]. These results may indicate the elevation of LPL activity ameliorate obesity.

Therefore, we hypothesized that elevating LPL activity would cause an improvement of cachexia and obesity. To test this hypothesis, we studied the effects of the LPL activator NO-1886 in cachexia and obese animals.

Lipoprotein Lipase (LPL)

LPL is a glycoprotein located on the luminal surface of capillary endothelial cells. The active enzyme is a nonconvalent homodimer [13]. The enzyme has an apparent monometric molecular mass of 60,000 daltons on SDS-PAGE. The human LPL gene is approximately 30 kb in length [14].

LPL mRNA has been found in human adipose tissue, and also in muscle, adrenal, kidneys, intestine and neonatal, but not adult liver. The mRNA for LPL in humans is highly homologus with that of mice, rats and cows [15,16].

LPL binds to heparin sulfate [17] on the surface of endothelial cells via the heparin-binding site, which allows the enzyme to be extended into the plasma [18]. Following intravenous administration of heparin, LPL can be displaced from the endothelial surface into plasma (post-heparin plasma), where enzyme activity can be measured. The active enzyme bound to heparin sulfate on the capillary endothelium is predominantly in the dimeric form.

TGs and monoglycerides are preferred substrates for LPL, which preferentially hydrolyzes 1- and 3- ester bounds in TGs, generating 2-monoglycerides, which are converted to 1-monoglycerides by isomerization for further hydrolysis [19]. A small portion of the core TG from chylomicron and very-low-density lipoprotein (VLDL) can be transferred to HDL. More important contributors to high density lipoprotein (HDL) are the surface remnants of the TG-rich lipoproteins that occur as a result of hydrolysis of core TG. Nikkila et al. have noted

***Corresponding author:** Masataka Kusunoki, Department of Internal Medicine, Medical Clinic, Aichi Medical University, 2-12-1, Higashisakura, Higashi-ku, Nagoya 461-0005, Japan, Tel: +81-52-931-2261; Fax: +81-52-931-4841; E-mail: info@tonyo.jp

Received May 20, 2013; **Accepted** May 31, 2013; **Published** June 03, 2013

Citation: Kusunoki M, Tsutsumi K, Tana C, Sato D, Nakamura T (2013) Lipoprotein Lipase Activation Improves the Cachexia and Obesity. J Obes Weight Loss Ther 3: 177. doi:10.4172/2165-7904.1000177

a relationship between LPL activity and HDL-C, especially HDL_2 cholesterol (HDL_2-C), in many clinical situations [20]. Tsutsumi et al. [21] reported that plasma TG levels were inversely correlated with post-heparin plasma LPL activity, while HDL-C levels were positively correlated with the activity of the enzyme in rats.

Insulin increases LPL activity, rates of LPL synthesis and LPL mRNA levels in adipocytes [22]. Since insulin does not stimulate LPL gene transcription [13], the increases in steady-state LPL mRNA must be due to changes in mRNA stability (post-transcriptional mechanism).

Insulin-deficient diabetes results in a reduced degradation of VLDL by the reduction of functional (endothelium-bound) LPL activity in myocardium and adipose tissue, and short-term administration of insulin in vivo restores the effects of LPL activity in adipose tissue, but not in myocardium [23].

Whether LPL directly or indirectly promotes or protects against atherosclerosis remains controversial. Misenbock et al. [24] reported that LPL +/- humans have atherogenic lipoproteins, especially in the postprandial state. Katzel et al. [25] found that older, normocholesterolemic, nondiabetic athletic individuals with silent myocardial ischemia have increased insulin resistance, increased post-heparin plasma hepatic triglyceride lipase (HTGL) activity and reduced postprandial response of abdominal adipose tissue LPL activity to feeding. These conditions are associated with low HDL_2-C levels and increased postprandial lipemia. The abnormalities in plasma HDL-C and postprandial TG metabolism may increase the risk for coronary artery disease in these subjects.

Reymer et al. [26] studied human LPL mutations. They showed that in approximately 1 in 20 males with proven atherosclerosis, an Asn291Ser mutation in the human LPL gene is associated with significantly reduced plasma HDL-C concentrations and results in a significant decrease in LPL catalytic activity. They showed the relationship between LPL activity and plasma HDL-C concentrations, and suggested that a specific LPL mutation may be a factor in the development of atherosclerosis.

Higher levels of post-heparin plasma LPL activity are associated with decrease plasma TG and increased HDL-C [21]. People who are heterozygous for LPL deficiency have increased plasma TG and decreased plasma HDL-C concentrations, a profile associated with increased atherogenic risk [27]. These reports suggest that increased post-heparin plasma LPL activity is associated post-heparin plasma LPL activity is associated with protection against atherosclerosis in humans.

Fan et al. [28] generated transgenic rabbits expressing human LPL to elucidate the physiological roles of LPL in lipid and lipoprotein metabolism. When the transgenic rabbits were fed a cholesterol-rich diet, the development of hypercholesterolemia and aortic atherosclerosis was dramatically suppressed. Using another model, Shimada et al. [29] established an over expressed human LPL gene in the heart, skeletal muscle and adipose tissue of mice. These transgenic mice had 5- and 1.7-fold higher LPL activity in adipose tissue and post-heparin plasma, respectively. Also, VLDL triglycerides were greatly reduced and HDL_2 was increased 1.4-fold. These results demonstrated that the lipid profile in these LPL transgenic mice is antiatherogenic.

Shimada et al. [30] also created LDL receptor knockout mice (LDLRKO) that overexpressd LPL (LPL/LDLRKO) by mating LPL transgenic mice to LDLRKO mice, and compared their plasma lipoprotein profiles and atherosclerosis with those in nonexpressing LDLRKO mice. LPL/LDLRKO mice showed marked suppression of mean plasma TG concentrations and a modest decrease in cholesterol concentrations compared to LDLRKO mice. Thus, it was showed that the altered lipoprotein profile, in particular the reduced level of remnant lipoproteins exerts protection by LPL against atherosclerosis.

Regarding the LPL activator NO-1886, NO-1886 were significantly dose-dependent increases in post-heparin plasma LPL activity in normal rats [21]. On the other hand, NO-1886 did not affect post-heparin plasma HTGL. NO-1886 also significantly and dose-dependently increased tissue LPL activity in normal rats. NO-1886 enhanced expression of LPL mRNA in adipose tissue and myocardium, and increased LPL protein mass and LPL activity in post-heparin plasma [21].

NO-1886 was significantly dose-dependent decrease in plasma TG levels, with concomitant increase in plasma HDL-C in rats, hamsters and rabbits [31]. Endothelial function is closely related to the development of atherosclerosis and is impaired before the development of initial lesions in hypercholesterolemic animals [32]. Aging is associated with a progressive development of dyslipidemia, insulin resistance and obesity, all of which are risk factors for cardiovascular disease and atherosclerosis [33]. It is known that endothelium-dependent relaxation decreases with age [34]. Previously, we reported that NO-1886 ameliorated the aging-related deterioration of endothelium-dependent relaxation in thoracic aorta in 10-month-old male rats [35]. We also reported that NO-1886 prevented the development of impaired endothelium-dependent relaxation of rat thoracic aorta in 2-year-old male rats [36]. These groups speculated that NO-1886 might have improved the endothelium-dependent relaxation by normalizing the lipid disorder, in particular by elevating plasma HDL-C, which possesses antioxidant effects [37] and is very important in exercised old rats due to elevated plasma lipid peroxide levels caused by exercise [36]. Long-term administration of NO-1886 to rats with experimental atherosclerosis caused by a high-cholesterol diet significantly inhibited the development of atherosclerotic lesions in the coronary arteries [21]. The results of multiple regression analysis in the studies suggest that plasma HDL-C is a strong protective factor against atherosclerosis in coronary arteries. Chiba et al. [38] administered NO-1886 to cholesterol-fed New Zealand white rabbits for 20 weeks. NO-1886 increased post-heparin plasma LPL activity 30-40% compared with the control group. Plasma HDL-C concentrations were 2-fold greater in the NO-1886 group compared to in the controls, and plasma TG was reduced to the level of normal controls. Post-heparin plasma LPL activity was positively correlated with plasma HDL-C and inversely correlated with plasma TG. The relative atheomatous area in the aorta was reduced to 11-14% in the NO-1886 group compared to 51% in the control group. Multiple regression analysis of post-heparin plasma LPL activity, plasma HDL-C and TG indicated that plasma HDL-C was the most powerful protector against aortic cholesterol accumulation. A decrease in plasma TG also protected against atherosclerosis, though not as strongly as plasma HDL-C. They concluded that NO-1886 prevented the development of atherosclerosis by increasing LPL activity, resulting in an increase in plasma HDL-C and a decrease in plasma TG, without a significant influence of plasma total cholesterol concentrations.

Yin et al. [39] created a diabetic rabbit model with atherosclerosis in the aorta by feeding a high-fat/high-sucrose diet. They administered NO-1886 to these rabbits to determine whether the LPL activator had an antiatherogenic effect. NO-1886 decreased plasma cholesterol and

TG, and increased plasma HDL-C. Interestingly, NO-1886 provided protection against the development of atherosclerosis in the aorta. These results suggest that NO-1886 not only ameliorates the lipid disorder but also lower plasma glucose levels and suppresses atherosclerosis in the aorta of diabetic rabbits.

These published papers show that activation of LPL protects against the development of atherosclerosis.

Cachexia

Cachexia is defined as an extreme wasting condition with marked weight loss, anorexia, and lassitude [1]. It is observed in patients with cancer and severe infectious disease, and is a terminal manifestation of these diseases. About half of all cancer patients show a syndrome of cachexia characterized by loss of adipose tissue and skeletal muscle mass. Such patients have a decreased survival time compared with that of patients without weight loss [2]. Adipose tissue atrophy is marked in cachectic patients and animals. Fat deposition is accomplished by the action of LPL in adipose tissue and by de novo lipogenesis in the liver and adipose tissue [40]. LPL activity in adipose tissue has been reported to be depressed in tumor-bearing animals [40-42]. Vlassara et al. reported that LPL activity in cancer patients was lower than in healthy persons and that the degree of the decrease was closely correlated with the degree of weight loss when LPL activity was determined in the post-heparin plasma of these patients [43].

Research on cytokines and cachexia has advanced, and it has become clear that certain cytokines are involved in the onset of cachexia [3,44]. TNF [3,44], IL-1 [45] and IL-6 [46], in particular, are thought to inhibit the activity of LPL, thereby suppressing hydrolysis of VLDL-TG, decreasing the supply of NEFA to adipose tissue, and eventually inducing weight loss as a result of a reduction of fat accumulation in the tissue. LPL activity is reported to decrease as the tumor burden increases in tumor-bearing animals and patients with lung cancer, thus LPL is suggested to be the mechanism inducing the decrease in fat depots in cancer patients [41,42,47].

Cachexia patients and cancer-bearing animals show decrease in LPL activity in postheparin plasma and adipose tissue, and a number of reports have indicated that the decrease in LPL activity is presumably attributable to the emaciation in cachexia [40-43]. This suggests that emaciation can be prevented and cachexia improved by suppressing the decrease in LPL activity. Ohara et al. [48] therefore administrated an LPL activator NO-1886, to a rat model of cachexia to investigate its effects [48].

Obeid et al. have reported that the Leydig cell tumor is a model that resembles human cachexia rather well, because the tumor induced slow progression of anorexia, as well as marked weight loss [49]. Sabatini et al. [50] have reported that Leydig cell tumors produce TNF and that TNF induces cachexia. Therefore, LPL activator NO-1886 administered to Leydig cell tumor-bearing rats may have beneficial effects. When Leydig cells were inoculated into rats, there was an early decrease in plasma total protein and albumin levels after inoculation, followed by a decrease in plasma glucose and HDL-C, with the animals showing signs of malnutrition throughout. Food consumption decreased after tumor inoculation, and thereafter the rats rapidly grew leaner. LPL activity in rat adipose tissue and adipose tissue weight were decreased by Leydig cell inoculation. NO-1886 prevented the decrease in carcass weight and malnutrition resulting from the appetite suppression attributable to Leydig cell tumors. From these results, the LPL activator is considered to be potentially beneficial for the treatment of cancer cachexia and other wasting syndromes.

Also, anticancer drugs have side effect such as appetite suppression and reduction of body weight. Therefore, combination therapy with anticancer drugs and an LPL activator may result in suppression of the side effects.

Obesity

Obesity in adulthood is characterized by adipocyte hypertrophy. Adipose tissue participates in the regulation of energy homeostasis. High-fat diet-induced insulin resistance associated with obesity is a major risk factor for diabetes and cardiovascular disease [10]. Adipose tissue itself serves as the site of triglyceride (TG) storage and free fatty acid release in response to changing energy demands [10]. Adipose tissue also participates in the regulation of energy homeostasis as an important endocrine organ that secretes a number of biologically active adipokines such as adipsin [51], leptin [52], plasminogen activator inhibitor-1 [53], resistin [54], TNF-α [55], and adiponectin [56]. LPL is one such adipokine.

LPL plays a pivotal role in lipids and the metabolism of lipoprotein [11]. Major functions of LPL include the hydrolysis of TG-rich lipoproteins and release of NEFA, which are taken up and used for metabolic energy in peripheral tissue such as muscle, or are re-esterified into TG and stored in adipose tissue. The balance between these competing effects could determine whether increased LPL activity will lead to a reduced rate of weight gain or to increased adiposity through increased rates of adipose tissue storage of TG.

Some reports have suggested that LPL activity in adipose tissue is high in obesity [57,58]. An imbalance of LPL activity may alter the partitions of plasma TG between muscle and adipose tissue, and thus influence insulin resistance and obesity.

Shimada et al. [59] have reported that none of the mice in which human LPL gene expression was induced became obese, and that storage and decomposition of fat were balanced in mice as a result of increased activity of hormone-sensitive lipase in adipose tissue. In other words, because of homeostasis body weight may not be increased in normal animals even by elevation of LPL activity.

Jensen et al. [60] have reported that overexpression of human LPL in skeletal muscle prevents diet-induced obesity in transgenic mice. Accordingly to Ferraro et al. [61] the RQ is inversely correlated with LPL activity in skeletal muscle in Pima Indians, and Pima Indians have a high RQ, which is a risk factor for body weight gain.

Hara et al. [12] have also reported that long term administration of LPL activator NO-1886 causes a reduction in RQ in high-fructose-induced diabetic rats without fat accumulation in tissues. The RQ is the steady-state ration of carbon dioxide production to oxygen consumption by whole-body tissue metabolism. Therefore, in general, a decrease in RQ means an increase in fatty oxidation. Based on this information, we hypothesized that an LPL activator may improve obesity by activating LPL in skeletal muscle.

NO-1886 was administered to rats rendered obese with a high-fat diet. NO-1886 suppressed the body weight gain and accumulation of visceral and subcutaneous fat. NO-1886 also increased skeletal muscle LPL activity without affecting adipose tissue LPL activity, and lowered the RQ in obese rats [62].

It has long been known that uncoupling proteins (UCPs) are responsible for facultative thermogenesis in rodents. UCPs play an important role in energy metabolism and obesity [63]. UCP1 expression is restricted to brown adipose tissue (BAT), UCP2 is widely

expressed, and UCP3 is found mainly in skeletal muscle [64]. Doi et al. [65] have reported that NO-1886 accelerates the expression of fatty acid oxidation-related enzymes, resulting in a reduction of RQ. However, the mechanism for antiobesity effects of NO-1886 remained unclear. To clarify the mechanism, we studied the effects of NO-1886 on the expression of UCP1, UCP2, and UCP3 in rats [66]. NO-1886 did not affect the expression of UCP1 and UCP2 in BAT, mesenteric adipose tissue, and skeletal muscle, but NO-1886 increased the expression of UCP3 mRNA only in skeletal muscle. Therefore, a possible mechanism for NO-1886′s antiobesity effects in rats may be the enhancement of LPL activity in skeletal muscle and the accompanying increase in UCP3 expression.

The antidiabetic agent pioglitazone is thought to promote the differentiation of adipocytes, convert large-type hypertrophic adipocytes into small-type adipocytes, and to increase insulin activity through peroxisome proliferator-activated receptor-gamma activation [67]. In addition, thiazolidinediones have also been shown to improve the serum levels of several adiopocytokines, such as adiponection and TNF-α, in type 2 diabetic patients [68]. However, as a result of enhanced adipocyte differentiation, pioglitazone treatment has been shown to be associated with body weight gain in obese animals and type 2 diabetic patients [68-70]. As the mechanism underlying the body weight gain, Hallakou et al. [71] explained that pioglitazone stimulated the expression of genes involved in lipid metabolism and induced a large increase in glucose utilization in the adipose tissue. Obesity aggravates diabetes and promotes cardiovascular diseases and atherosclerosis, and the body-weight-increasing action of pioglitazone is a disadvantage in diabetic patients. On the other hand, the LPL activator is known to improve both obesity and insulin resistance in obese animals [62,66].

Recently, we investigated the effect of the simultaneous administration of pioglitazone, which induces a body weight gain, and NO-1886, which has an anti-obesity action, on the body weight and insulin resistance of obese rats [72]. The concomitant administration of pioglitazone and NO-1886 suppressed the body weight gain in animals fed a high-fat diet, confirming that NO-1886 mitigates the body weight-increasing action of pioglitazone. Since an assessment of their effects on insulin resistance showed that both pioglitazone and NO-1886 treated to increase the glucose infusion rate (GIR) in obese animals, these compounds may also improve insulin resistance. The percent increase in the GIR in the pioglitazone + NO-1886 group was greater than that in either the pioglitazone or the NO-1886 group. Consequently, the improvement of insulin sensitivity may be enhanced by the combined administration of pioglitazone and NO-1886, compared with that observed following the administration of either drug alone. Thus, the combined administration of pioglitazone and LPL activator may be of great benefit for the treatment of type 2 diabetic patients.

Profile of LPL activator NO-1886 (ibrolipim) is shown in Table 1.

Conclusions

The main LPL synthetic tissues are adipose tissue and muscle. LPL in adipose tissue has a role in fat storage, where LPL in skeletal muscle has a role in fatty oxidation. Therefore, if adipose tissue-specific LPL activators and skeletal muscle-specific LPL activators are developed, we may be able to design anticachexic and antiobesity drugs. LPL activator NO-1886 improved cancer cachexia by elevating adipose tissue LPL activity, and it improved obesity by elevating skeletal muscle LPL activity. We expect further evaluation of tissue-specific LPL activators may also show a clinically relevant benefit in the treatment of lipid-associated and non-lipid-associated diseases.

LPL activity	Post-heparin plasma	Activation
	Adipose tissue	Activation
	Skeletal muscle	Activation
	Myocardium	Activation
LPL mRNA		Enhancing
LPL mass		Increasing
Plasma lipid	HDL cholesterol	Increasing
	Triglyceride	Reduction
	Total cholesterol	No effects of elevation
	Free fatty acid	No effects of reduction
Atherosclerosis	Coronary artery	Protection
	Aortae	Protection
Type 2 diabetes	Blood glucose	Reduction
	Plasma insulin	Reduction
	Insulin resistance	Improvement
Diabetic cataracts		Improvement
Fatty liver in diabetes	Lipids contents	Reduction
Obesity	Body weight	Reduction
	Respiratory quotient	Reduction
	Insulin resistance	Improvement
Uncoupling protein (UCP)	UCP1 mRNA	No effects
	UCP2 mRNA	No effects
	UCP3 mRNA	Increasing
Cachexia	Body weight	Increasing
	Food consumption	Increasing

Table 1: Profile of LPL activator NO-1886 (ibrolipim) in animals.

References

1. Theologides A (1979) Cancer cachexia. Cancer 43: 2004-2012.
2. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, et al. (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 69: 491-497.
3. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, et al. (1985) Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 316: 552-554.
4. Gelin J, Moldawer LL, Lönnroth C, Sherry B, Chizzonite R, et al. (1991) Role of endogenous tumor necrosis factor alpha and interleukin 1 for experimental tumor growth and the development of cancer cachexia. Cancer Res 51: 415-421.
5. Oliff A, Defeo-Jones D, Boyer M, Martinez D, Kiefer D, et al. (1987) Tumors secreting human TNF/cachectin induce cachexia in mice. Cell 50: 555-563.
6. Mori M, Yamaguchi K, Honda S, Nagasaki K, Ueda M, et al. (1991) Cancer cachexia syndrome developed in nude mice bearing melanoma cells producing leukemia-inhibitory factor. Cancer Res 51: 6656-6659.
7. Matthys P, Dijkmans R, Proost P, Van Damme J, Heremans H, et al. (1991) Severe cachexia in mice inoculated with interferon-gamma-producing tumor cells. Int J Cancer 49: 77-82.
8. Matthys P, Heremans H, Opdenakker G, Billiau A (1991) Anti-interferon-gamma antibody treatment, growth of Lewis lung tumours in mice and tumour-associated cachexia. Eur J Cancer 27: 182-187.
9. Strassmann G, Jacob CO, Evans R, Beall D, Fong M (1992) Mechanisms of experimental cancer cachexia. Interaction between mononuclear phagocytes and colon-26 carcinoma and its relevance to IL-6-mediated cancer cachexia. J Immunol 148: 3674-3678.
10. Spiegelman BM, Flier JS (1996) Adipogenesis and obesity: rounding out the big picture. Cell 87: 377-389.
11. Goldberg IJ (1996) Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res 37: 693-707.
12. Hara T, Cameron-Smith D, Cooney GJ, Kusunoki M, Tsutsumi K, et al. (1998) The actions of a novel lipoprotein lipase activator, NO-1886, in hypertriglyceridemic fructose-fed rats. Metabolism 47: 149-153.

13. Peterson J, Fujimoto WY, Brunzell JD (1992) Human lipoprotein lipase: relationship of activity, heparin affinity, and conformation as studied with monoclonal antibodies. J Lipid Res 33: 1165-1170.

14. Sparkes RS, Zollman S, Klisak I, Kirchgessner TG, Komaromy MC, et al. (1987) Human genes involved in lipolysis of plasma lipoproteins: mapping of loci for lipoprotein lipase to 8p22 and hepatic lipase to 15q21. Genomics 1: 138-144.

15. Wion KL, Kirchgessner TG, Lusis AJ, Schotz MC, Lawn RM (1987) Human lipoprotein lipase complementary DNA sequence. Science 235: 1638-1641.

16. Senda M, Oka K, Brown WV, Qasba PK, Furuichi Y (1987) Molecular cloning and sequence of a cDNA coding for bovine lipoprotein lipase. Proc Natl Acad Sci U S A 84: 4369-4373.

17. Clarke AR, Luscombe M, Holbrook JJ (1983) The effect of the chain length of heparin on its interaction with lipoprotein lipase. Biochim Biophys Acta 747: 130-137.

18. Pedersen ME, Cohen M, Schotz MC (1983) Immunocytochemical localization of the functional fraction of lipoprotein lipase in the perfused heart. J Lipid Res 24: 512-521.

19. Brunzell JD (1995) Familial lipoprotein lipase deficiency and other causes of chylomicromia syndrome: The metabolic and molecular bases of inherited disease. McGraw-Hill, New York.

20. Nikkilä EA, Taskinen MR, Kekki M (1978) Relation of plasma high-density lipoprotein cholesterol to lipoprotein-lipase activity in adipose tissue and skeletal muscle of man. Atherosclerosis 29: 497-501.

21. Tsutsumi K, Inoue Y, Shima A, Iwasaki K, Kawamura M, et al. (1993) The novel compound NO-1886 increases lipoprotein lipase activity with resulting elevation of high density lipoprotein cholesterol, and long-term administration inhibits atherogenesis in the coronary arteries of rats with experimental atherosclerosis. J Clin Invest 92: 411-417.

22. Raynolds MV, Awald PD, Gordon DF, Gutierrez-Hartmann A, Rule DC, et al. (1990) Lipoprotein lipase gene expression in rat adipocytes is regulated by isoproterenol and insulin through different mechanisms. Mol Endocrinol 4: 1416-1422.

23. Tsutsumi K, Inoue Y, Shima A, Murase T (1995) Correction of hypertriglyceridemia with low high-density lipoprotein cholesterol by the novel compound NO-1886, a lipoprotein lipase-promoting agent, in STZ-induced diabetic rats. Diabetes 44: 414-417.

24. Miesenböck G, Hölzl B, Föger B, Brandstätter E, Paulweber B, et al. (1993) Heterozygous lipoprotein lipase deficiency due to a missense mutation as the cause of impaired triglyceride tolerance with multiple lipoprotein abnormalities. J Clin Invest 91: 448-455.

25. Katzel LI, Busby-Whitehead MJ, Rogus EM, Krauss RM, Goldberg AP (1994) Reduced adipose tissue lipoprotein lipase responses, postprandial lipemia, and low high-density lipoprotein-2 subspecies levels in older athletes with silent myocardial ischemia. Metabolism 43: 190-198.

26. Reymer PW, Gagné E, Groenemeyer BE, Zhang H, Forsyth I, et al. (1995) A lipoprotein lipase mutation (Asn291Ser) is associated with reduced HDL cholesterol levels in premature atherosclerosis. Nat Genet 10: 28-34.

27. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE (1997) Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 96: 2520-2525.

28. Fan J, Unoki H, Kojima N, Sun H, Shimoyamada H, et al. (2001) Overexpression of lipoprotein lipase in transgenic rabbits inhibits diet-induced hypercholesterolemia and atherosclerosis. J Biol Chem 276: 40071-40079.

29. Shimada M, Shimano H, Gotoda T, Yamamoto K, Kawamura M, et al. (1993) Overexpression of human lipoprotein lipase in transgenic mice. Resistance to diet-induced hypertriglyceridemia and hypercholesterolemia. J Biol Chem 268: 17924-17929.

30. Shimada M, Ishibashi S, Inaba T, Yagyu H, Harada K, et al. (1996) Suppression of diet-induced atherosclerosis in low density lipoprotein receptor knockout mice overexpressing lipoprotein lipase. Proc Natl Acad Sci U S A 93: 7242-7246.

31. Tsutsumi K, Inoue Y, Hagi A, Murase T (1997) The novel compound NO-1886 elevates plasma high-density lipoprotein cholesterol levels in hamsters and rabbits by increasing lipoprotein lipase without any effect on cholesteryl ester transfer protein activity. Metabolism 46: 257-260.

32. Shimokawa H, Vanhoutte PM (1989) Impaired endothelium-dependent relaxation to aggregating platelets and related vasoactive substances in porcine coronary arteries in hypercholesterolemia and atherosclerosis. Circ Res 64: 900-914.

33. Lakatta EG, Yin FC (1982) Myocardial aging: functional alterations and related cellular mechanisms. Am J Physiol 242: H927-941.

34. Moritoki H, Tanioka A, Maeshiba Y, Iwamoto T, Ishida Y, et al. (1988) Age-associated decrease in histamine-induced vasodilation may be due to reduction of cyclic GMP formation. Br J Pharmacol 95: 1015-1022.

35. Hara T, Kusunoki M, Tsutsumi K, Okada K, Sakamoto S, et al. (1998) A lipoprotein lipase activator, NO-1886, improves endothelium-dependent relaxation of rat aorta associated with aging. Eur J Pharmacol 350: 75-79.

36. Kusunoki M, Tsutsumi K, Hara T, Ogawa H, Nakamura T, et al. (2002) A lipoprotein lipase activator, NO-1886 prevents impaired endothelium-dependent relaxation of aorta caused by exercise in aged rats. Exp Gerontol 37: 891-896.

37. Ohta T, Takata K, Horiuchi S, Morino Y, Matsuda I (1989) Protective effect of lipoproteins containing apoprotein A-I on Cu2+-catalyzed oxidation of human low density lipoprotein. FEBS Lett 257: 435-438.

38. Chiba T, Miura S, Sawamura F, Uetsuka R, Tomita I, et al. (1997) Antiatherogenic effects of a novel lipoprotein lipase-enhancing agent in cholesterol-fed New Zealand white rabbits. Arterioscler Thromb Vasc Biol 17: 2601-2608.

39. Yin W, Tsutsumi K, Yuan Z, Yang B (2002) Effects of the lipoprotein lipase activator NO-1886 as a suppressor agent of atherosclerosis in aorta of mild diabetic rabbits. Arzneimittelforschung 52: 610-614.

40. Thompson MP, Koons JE, Tan ET, Grigor MR (1981) Modified lipoprotein lipase activities, rates of lipogenesis, and lipolysis as factors leading to lipid depletion in C57BL mice bearing the preputial gland tumor, ESR-586. Cancer Res 41: 3228-3232.

41. Evans RD, Williamson DH (1988) Tissue-specific effects of rapid tumour growth on lipid metabolism in the rat during lactation and on litter removal. Biochem J 252: 65-72.

42. Lanza-Jacoby S, Miller EE, Rosato FE (1982) Changes in the activities of lipoprotein lipase and the lipogenic enzymes in tumor-bearing rats. Lipids 17: 944-949.

43. Vlassara H, Spiegel RJ, San Doval D, Cerami A (1986) Reduced plasma lipoprotein lipase activity in patients with malignancy-associated weight loss. Horm Metab Res 18: 698-703.

44. Kawakami M, Cerami A (1981) Studies of endotoxin-induced decrease in lipoprotein lipase activity. J Exp Med 154: 631-639.

45. Moldawer LL, Georgieff M, Lundholm K (1987) Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia. Clin Physiol 7: 263-274.

46. Beck SA, Tisdale MJ (1991) Lipid mobilising factors specifically associated with cancer cachexia. Br J Cancer 63: 846-850.

47. Mori M, Yamaguchi K, Abe K (1989) Purification of a lipoprotein lipase-inhibiting protein produced by a melanoma cell line associated with cancer cachexia. Biochem Biophys Res Commun 160: 1085-1092.

48. Ohara M, Tsutsumi K, Ohsawa N (1998) Suppression of carcass weight loss in cachexia in rats bearing Leydig cell tumor by the novel compound NO-1886, a lipoprotein lipase activator. Metabolism 47: 101-105.

49. Obeid OA, Emery PW (1993) Lipid metabolism in cachectic tumor-bearing rats at different stages of tumor growth. Nutr Cancer 19: 87-98.

50. Sabatini M, Yates AJ, Garrett IR, Chavez J, Dunn JF, et al. (1990) Increased production of tumor necrosis factor by normal immune cells in a model of the humoral hypercalcemia of malignancy. Lab Invest 63: 676-682.

51. White RT, Damm D, Hancock N, Rosen BS, Lowell BB, et al. (1992) Human adipsin is identical to complement factor D and is expressed at high levels in adipose tissue. J Biol Chem 267: 9210-9213.

52. Friedman JM (2000) Obesity in the new millennium. Nature 404: 632-634.

53. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, et al. (1996) Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med 2: 800-803.

54. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. (2001) The hormone resistin links obesity to diabetes. Nature 409: 307-312.

55. Hotamisligil GS (1999) The role of TNFalpha and TNF receptors in obesity and insulin resistance. J Intern Med 245: 621-625.

56. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF (1995) A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 270: 26746-26749.

57. Kern PA, Ong JM, Saffari B, Carty J (1990) The effects of weight loss on the activity and expression of adipose-tissue lipoprotein lipase in very obese humans. N Engl J Med 322: 1053-1059.

58. Sadur CN, Yost TJ, Eckel RH (1984) Insulin responsiveness of adipose tissue lipoprotein lipase is delayed but preserved in obesity. J Clin Endocrinol Metab 59: 1176-1182.

59. Shimada M, Ishibashi S, Yamamoto K, Kawamura M, Watanabe Y, et al. (1995) Overexpression of human lipoprotein lipase increases hormone-sensitive lipase activity in adipose tissue of mice. Biochem Biophys Res Commun 211: 761-766.

60. Jensen DR, Schlaepfer IR, Morin CL, Pennington DS, Marcell T, et al. (1997) Prevention of diet-induced obesity in transgenic mice overexpressing skeletal muscle lipoprotein lipase. Am J Physiol 273: R683-689.

61. Ferraro RT, Eckel RH, Larson DE, Fontvieille AM, Rising R, et al. (1993) Relationship between skeletal muscle lipoprotein lipase activity and 24-hour macronutrient oxidation. J Clin Invest 92: 441-445.

62. Kusunoki M, Hara T, Tsutsumi K, Nakamura T, Miyata T, et al. (2000) The lipoprotein lipase activator, NO-1886, suppresses fat accumulation and insulin resistance in rats fed a high-fat diet. Diabetologia 43: 875-880.

63. Boss O, Muzzin P, Giacobino JP (1998) The uncoupling proteins, a review. Eur J Endocrinol 139: 1-9.

64. Schrauwen P, Hesselink M (2002) UCP2 and UCP3 in muscle controlling body metabolism. J Exp Biol 205: 2275-2285.

65. Doi M, Kondo Y, Tsutsumi K (2003) Lipoprotein lipase activator NO-1886 (ibrolipim) accelerates the mRNA expression of fatty acid oxidation-related enzymes in rat liver. Metabolism 52: 1547-1550.

66. Kusunoki M, Tsutsumi K, Iwata K, Yin W, Nakamura T, et al. (2005) NO-1886 (ibrolipim), a lipoprotein lipase activator, increases the expression of uncoupling protein 3 in skeletal muscle and suppresses fat accumulation in high-fat diet-induced obesity in rats. Metabolism 54: 1587-1592.

67. Spiegelman BM (1998) PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. Diabetes 47: 507-514.

68. Miyazaki Y, DeFronzo RA (2008) Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokines in type 2 diabetic patients. Diabetes Obes Metab 10: 1204-1211.

69. Boden G, Zhang M (2006) Recent findings concerning thiazolidinediones in the treatment of diabetes. Expert Opin Investig Drugs 15: 243-250.

70. Hermansen K, Mortensen LS (2007) Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. Drug Saf 30: 1127-1142.

71. Hallakou S, Doaré L, Foufelle F, Kergoat M, Guerre-Millo M, et al. (1997) Pioglitazone induces in vivo adipocyte differentiation in the obese Zucker fa/fa rat. Diabetes 46: 1393-1399.

72. Kusunoki M, Tsutsumi K, Sato D, Nakamura A, Habu S, et al. (2011) Pioglitazone-induced body weight gain is prevented by combined administration with the lipoprotein lipase activator NO-1886. Eur J Pharmacol 668: 486-491.