Mechanism of Action of Fibrates on Lipid and Lipoprotein Metabolism

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Abstract—Treatment with fibrates, a widely used class of lipid-modifying agents, results in a substantial decrease in plasma triglycerides and is usually associated with a moderate decrease in LDL cholesterol and an increase in HDL cholesterol concentrations. Recent investigations indicate that the effects of fibrates are mediated, at least in part, through alterations in transcription of genes encoding for proteins that control lipoprotein metabolism. Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs). The PPAR-α form mediates fibrate action on HDL cholesterol levels via transcriptional induction of synthesis of the major HDL apolipoproteins, apoA-I and apoA-II. Fibrates lower hepatic apoC-III production and increase lipoprotein lipase—mediated lipolysis via PPAR. Fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the β-oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, results in a decrease in VLDL production. In summary, both enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on HDL metabolism is associated with changes in HDL apolipoprotein expression. **(*Circulation*. 1998;98:2088-2093.)**

Key Words: apolipoproteins ■ arteriosclerosis ■ fibrates ■ hypercholesterolemia ■ hyperlipoproteinemia ■ lipids ■ PPAR

A vast number of studies confirmed the intimate and causative relationships between dyslipidemias and coronary heart disease. Although hypercholesterolemia is an important underlying cause for coronary heart disease, other dyslipidemias, such as hypoalphalipoproteinemia (low plasma HDL) and hypertriglyceridemia, may be causative in a substantial number of cases. Fibrates are useful for the treatment of hypoalphalipoproteinemia with or without hypertriglyceridemia.[1,2] The recommendation for the use of fibrates in certain types of dyslipidemia has gained additional support from a subgroup analysis of the Helsinki Heart Study,[3] which showed that the best preventive efficacy has been achieved in a subset of ≈10% of the study population who had a baseline LDL:HDL cholesterol ratio of >5 and a triglyceride level of 2.3 mmol/L.[4,5] Results from angiographic trials revealed that fibrates retard the progression of coronary atherosclerosis and decrease the number of coronary events.[6,7]

Pharmacological Action of Fibrates

Fibrates are generally effective in lowering elevated plasma triglycerides and cholesterol. The magnitude of lipid changes depends, however, on the patient's pretreatment lipoprotein status[8] as well as the relative potency of the fibrate used.[9] The most pronounced effects of fibrates are a decrease in plasma triglyceride-rich lipoproteins (TRLs). Levels of LDL cholesterol (LDL-C) generally decrease in individuals with elevated baseline plasma concentrations, and HDL cholesterol (HDL-C) levels are usually increased when baseline plasma concentrations are low.[8] However, paradoxical increases in LDL-C have been reported in some patients with dyslipidemia.[10] Fibrate treatment results in a reduction of the LDL fraction of atherogenic small, dense particles with an equivalent increase in the intermediate subfraction.[11–13] Within the triglyceride-rich apolipoprotein (apo) B-containing lipoproteins, fibrates efficiently reduce the apoC-III–containing particles,[14,15] which are markers for increased risk for atherogenesis.[16] The increased HDL concentrations after fibrates are generally reflected by increased plasma levels of apoA-I and apoA-II,[14,15] a change that is associated with an increase in lipoprotein (Lp) A-I:A-II, and a decrease in LpA-I concentrations in patients treated with fenofibrate.[14,15]

Mechanisms of Action of Fibrates

Evidence from studies in rodents and in humans is available to implicate 5 major mechanisms underlying the above-mentioned modulation of lipoprotein phenotypes by fibrates:

1. Induction of lipoprotein lipolysis. Increased TRL lipolysis could be a reflection of changes in intrinsic lipoprotein

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lipase (LPL) activity[17] or increased accessibility of TRLs for lipolysis by LPL owing to a reduction of TRL apoC-III content.[18]

2. Induction of hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production. In rodents, fibrates increase FA uptake and conversion to acyl-CoA by the liver owing to the induction of FA transporter protein (FATP)[19] and acyl-CoA synthetase (ACS) activity.[20] Induction of the β-oxidation pathway with a concomitant decrease in FA synthesis by fibrates results in a lower availability of FAs for triglyceride synthesis, a process that is amplified by the inhibition of hormone-sensitive lipase in adipose tissue by fibrates.[21]

3. Increased removal of LDL particles. Fibrate treatment results in the formation of LDL with a higher affinity for the LDL receptor, which are thus catabolized more rapidly.[11]

4. Reduction in neutral lipid (cholesteryl ester and triglyceride) exchange between VLDL and HDL may result from decreased plasma levels of TRL.[22]

5. Increase in HDL production and stimulation of reverse cholesterol transport. Fibrates increase the production of apoA-I and apoA-II in liver,[23,24] which may contribute to the increase of plasma HDL concentrations and a more efficient reverse cholesterol transport.

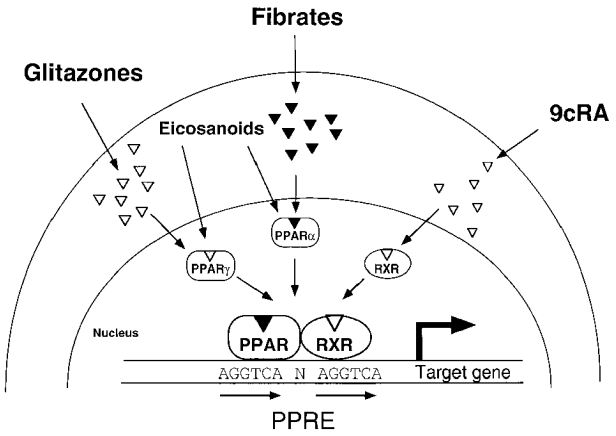
Role of Transcription Factors in Mediating Fibrate Action

It has been known for several years that fibrates induce peroxisome proliferation in rodents.[25,26] This process is linked to the induction of transcription of genes involved in peroxisomal β-oxidation and is mediated by specific transcription factors, therefore termed peroxisome proliferator-activated receptors (PPARs).

The PPAR Family of Transcription Factors

PPARs are members of the superfamily of nuclear hormone receptors, which are transcription factors transmitting signals that originate from lipid-soluble factors (eg, hormones, vitamins, and FAs) to the genome.[25,26] Nuclear receptors recognize and bind to DNA at specific sites, called response elements (REs), which consist of derivatives of the AGGTCA sequence. During evolution, mutation, duplication, and addition of flanking sequences have generated REs distinctive for the various receptors. Once bound to its RE, the receptor complex can activate or repress the expression of a target gene.

PPARs heterodimerize with the retinoid X receptor (RXR) and bind to REs arranged as direct repeats spaced by 1 nucleotide (DR1), termed peroxisome proliferator response elements (PPREs) (Figure). To date, 3 different PPAR genes (α, δ [also termed β, *NUC I*, or *FAAR*], and γ) have been identified.[25] PPARs display distinct expression patterns, which suggests important functional differences. PPAR-α is predominantly expressed in tissues that metabolize high amounts of FAs, such as liver, kidney, heart, and muscle.[27] The expression of PPAR-γ is high in adipose tissue, where it triggers adipocyte differentiation and induces the expression of genes critical for adipogenesis.[26]



The PPAR signaling pathway and its natural and synthetic activators. After activation by its respective ligands, PPARs heterodimerize with the receptor for 9*cis*-retinoic acid (9cRA), RXR, and bind to specific REs in the regulatory regions of target genes, termed PPREs, which are composed of 2 degenerate hexanucleotide repeats (arrows) arranged in tandem as direct repeats spaced by 1 nucleotide.

FAs and derivatives, such as prostaglandin J2 for PPAR-γ[28,29] or 8(S)hydroxyeicosatetraenoic acid,[30,31] 8(S)hydroxyeicosapentaenoic acid,[31] and leukotriene B4[32] for PPAR-α, have been implicated as natural PPAR ligands. Fibrates are synthetic ligands for PPAR-α.[30–32]

In rodents, fibrates induce the expression of genes involved in intracellular FA metabolism, such as peroxisomal and mitochondrial β-oxidation, ω-hydroxylation, and ketogenesis.[33] By contrast, very few data are available on the regulation of their human counterparts, and it awaits further study to determine whether fibrates and/or PPARs also regulate the expression of any of these genes in humans. However, in contrast to rodents, there is no evidence that fibrates would induce peroxisome proliferation in humans and primates.[34]

The Role of PPARs in Mediating Fibrate Action on Lipoprotein Metabolism in Humans

TRL Metabolism

The hypotriglyceridemic action of fibrates involves combined effects on LPL[17] and apoC-III expression,[34] resulting in increased lipolysis. The induction of LPL expression occurs at the transcriptional level and is mediated by PPAR. The latter binds to a PPRE that is present both in the human and the mouse LPL gene promoters.[35]

In contrast to LPL, transcription of the apoC-III gene is inhibited by fibrates, resulting in decreased production of apoC-III in the liver.[34] The repression of apoC-III gene expression by fibrates is mediated via PPAR-α.[36] Consistent with the repression of apoC-III expression, turnover studies in humans indicate that fibrates reduce apoC-III synthesis,[18] leading to enhanced LPL-mediated catabolism of VLDL particles. Moreover, fibrates also decrease apoB and VLDL production.[37] As a consequence, a reduced secretion of VLDL particles, together with the enhanced catabolism of triglyceride-rich particles, most likely accounts for the hypolipidemic effect of fibrates.

Animal studies suggest that fibrates also increase the hepatic uptake of free FAs (FFAs) by specific FATPs[19] and generation of acyl-CoA esters by ACS.[20] Owing to an

increased β-oxidation activity and a reduction in acetyl-CoA carboxylase and FA synthase activities,[38] FFA metabolism is shifted from triglyceride synthesis to catabolism. Although fibrates do not induce peroxisomal β-oxidation in humans, it is conceivable that they also affect FA uptake, conversion, and catabolism through the mitochondrial β-oxidation pathway in humans.

HDL Metabolism

In humans, fibrates increase plasma levels of HDL and its major constituents, apoA-I and apoA-II, to a variable extent[39,40] and stimulate apoA-I production in human apoA-I transgenic mice and human hepatocytes.[24] In vitro studies have demonstrated that the induction of human apoA-I gene expression after fibrates may be mediated by the interaction of PPAR with a functional PPRE, localized in the A site of the apoA-I promoter.[41] Human apoA-II plasma concentrations increase after fibrate treatment.[14,15] This is a consequence of the induction of hepatic apoA-II synthesis by fibrates and is mediated through PPAR/RXR heterodimers.[23]

Indications and Clinical Use of Fibrates in Specific Lipoprotein Disorders

Primary Hypertriglyceridemia

Fibrates are first-line drugs for the treatment of primary hypertriglyceridemia. In these patients, fibrates most noticeably decrease plasma TRLs[42]; they also decrease, albeit to a lesser extent, total cholesterol, whereas HDL-C levels increase.[42] The reduction in cholesterol and triglycerides is mainly due to a fall in VLDL, which is accompanied by changes in VLDL composition.[42] Fibrates predominantly reduce the concentrations of large VLDL subfractions.[43,44] In addition, fibrates attenuate the postprandial lipid response in hypertriglyceridemic subjects.[44]

LDL lipid composition is normalized in hypertriglyceridemic patients, who generally have low levels of LDL with an abnormal lipid composition.[45] The cholesteryl ester content of LDL increases in all LDL subclasses, resulting in large, less-dense LDL particles.[13,43] These changes lead to increased interactions of LDL particles with the LDL receptor, thereby improving LDL clearance.[46]

HDL-C levels, which are low in patients with hypertriglyceridemia, increase after treatment with fibrates.[42] The lowering of the pool of TRLs on treatment with fibrates results in the reduction of net cholesteryl ester transfer from HDL to TRLs,[22] which, in association with unchanged lecithin:cholesterol acyl transferase (LCAT) activity, will ultimately lead to an increase in cholesteryl ester and a decrease in triglyceride content of HDL. Improvement of LPL-mediated lipolysis of TRLs[43] and increased apoA-I and apoA-II synthesis may also contribute to the rise in HDL levels on treatment with fibrates by promoting the formation of HDL precursors.

Type III Dysbetalipoproteinemia

Type III dysbetalipoproteinemia is a rare lipid disorder resulting from homozygosity for the rare apoE2 isoform in predisposed subjects. The characteristic disturbance of this metabolic disorder is the accumulation of cholesterol-enriched VLDL, which migrates in β-position on agarose gel electrophoresis. Fibrates have a spectacular lipid-lowering potential in patients with type III dysbetalipoproteinemia.[15,47,48] The levels of circulating triglycerides and cholesterol are greatly diminished. The reduction in cholesterol is accounted for by the major reduction of VLDL cholesterol (VLDL-C) and IDL cholesterol, the most atherogenic lipoproteins in patients with type III dysbetalipoproteinemia. Simultaneously, LDL-C and HDL-C, which are usually low, increase significantly. As a consequence of the reduction in β-VLDL,[15] regression of xanthoma and improvement of manifestations of atherosclerosis are observed [49]

Combined Hyperlipidemia

Fibrates efficiently lower plasma cholesterol, VLDL-C, and triglycerides and increase HDL-C in combined hyperlipidemia.[50] The reduction in total cholesterol is accounted for by the fall in both VLDL-C and LDL-C,[51] whereas the reduction of triglyceride levels is associated with normalization of the typical atherogenic LDL subspecies profile in this lipid disorder. Fibrate treatment reduces the levels of dense LDL and of LDL-triglyceride content. Mean LDL peak particle size may increase to normal or remain small,[52] but the mean LDL flotation rate augments because of an increase in buoyant LDL concentration.[52]

Primary Hypercholesterolemia

Although fibrates are not considered to be first-line drugs in primary hypercholesterolemia,[1,2] the new generation of fibrates efficiently reduce plasma cholesterol and LDL-C and increase HDL-C concentrations when used in monotherapy in patients with primary hypercholesterolemia.[51,53] However, it should be emphasized that the response of hypercholesterolemic patients to fibrate treatment is heterogenous, and nonresponse or even a paradoxical increase in LDL has been observed.[54,55] The reduction in total cholesterol is accounted for by a fall in both VLDL-C and LDL-C.[53] Fibrates reduce the dense LDL but not the light LDL fraction,[56,57] which is less susceptible to oxidation.[13] The affinity of LDL for cellular receptors is not affected by treatment in patients with primary hypercholesterolemia.[57] The increase in HDL-C is related to a lower cholesteryl ester transfer protein activity, whereas LCAT activity is not affected.[57] In patients with primary hypercholesterolemia, LPL activity also increases on treatment with fibrates, resulting in a reduction of postprandial lipemia.[58]

Non–Insulin-Dependent Diabetes Mellitus

In non–insulin-dependent diabetes mellitus (NIDDM) with hyperlipemia, fibrates lower plasma cholesterol, triglycerides, VLDL, and IDL.[54,59–61] The levels of apoC-III decrease, resulting in improvement of TRL lipolysis and clearance.[59,62] The effect on LDL-C and apoB is dependent on the concentration of plasma TG.[54,60,61] The mean LDL particle diameter increases, whereas the concentration of dense LDL decreases in proportion to the changes in triglycerides.[63] Fibrates increase total HDL-C mainly owing to an elevation of the HDL_3 fraction.[62] As in patients with primary hyperlipemia, fibrates reduce postprandial lipemia in patients with NIDDM.[64]

Currently Available Fibrates and Their Pharmacological Characteristics

Drug	Maximum Dose	Usual Toxicity	Contraindications	Intervention Trials
Clofibrate	2000 mg/d	Myalgias; sporadically, rhabdomyolysis (may be aggravated by combination with statins); elevated transaminases (ASAT, ALAT); gallstone formation	Liver and renal insufficiency	WHO primary prevention trial: decreased incidence of myocardial infarction, but increased total mortality[71] not persisting in follow-up.[72] Newcastle and Edinburgh secondary prevention trials: decreased mortality in patients with angina.[73,74]
Gemfibrozil	1200 mg/d	Same as for clofibrate	Same as for clofibrate	HHS primary prevention trial: decreased cardiovascular but not total mortality,[3] highest benefit observed in overweight patients with LDL:HDL-C ratio >5 and triglycerides >2.3 mmol/L.[4,75] HIT secondary prevention trial: ends 2000.[76] LOCAT coronary angiography trial: retardation of progression of coronary atherosclerosis.[7]
Bezafibrate	600 mg/d	Same as for clofibrate	Same as for clofibrate	BIP secondary prevention trial: ends 1998.[77] BECAIT coronary angiography trial: retarded progression of coronary atherosclerosis.[6]
Fenofibrate	200 mg/d	Same as for clofibrate	Same as for clofibrate	FIELD primary and secondary prevention trial: start 1998; duration 5 y. DAIS coronary angiography trial: ends 1999.[78]
Ciprofibrate	100 mg/d	Same as for clofibrate	Same as for clofibrate	...

HHS indicates Helsinki Heart Study; HIT, High-density lipoprotein cholesterol Intervention Trial; LOCAT, Lopid Coronary Angiography Trial; BIP, Bezafibrate Infarction Prevention; BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; DAIS, Diabetes Atherosclerosis Intervention Study.

Tolerability and Safety

In general, fibrates are considered to be well tolerated, with an excellent safety profile. A low incidence of fibrate-associated toxicity has been reported in almost every organ system.[65] In accordance with this notion, a summary of 10 years' experience with fenofibrate with an exposure of 6 million patient-years including 7145 patients involved in clinical trials revealed a low frequency of side effects.[66]

Members of the 2 most popular classes of lipid-lowering drugs, HMG CoA reductase inhibitors and fibrates, cause cancer in rodents.[67] Although the mechanism may be related to peroxisome proliferation, a definite link has not yet been established. In humans, long-term administration of various fibrates does not cause peroxisome proliferation or any other morphological changes in the liver.[68,69] Extrapolation of this evidence of carcinogenesis from rodents to humans is uncertain.

Clinically relevant interactions of fibrates with other anti-hyperlipidemic drugs include rhabdomyolysis (reported in combination with HMG CoA reductase inhibitors) and decreased bioavailability when combined with some bile acid sequestrants. Finally, potentiation of the anticoagulant effect of coumarin derivatives may cause bleeding.[70]

Future Perspectives

The better understanding of the basic mechanisms of action of fibrates in both rodents and humans should now allow the development of novel compounds on a more rational basis. Because the currently available fibrates (Table) are rather nonspecific activators of various PPARs, it is expected that more potent and subtype-specific PPAR ligands and/or activators might constitute a novel class of "superfibrates." These compounds might enhance specificity, reduce side effects, and widen the clinical indications of this class of lipid-lowering drugs. Ongoing large clinical studies should confirm their effectiveness in reducing coronary events and demonstrate a possible benefit on coronary and total mortality.

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