Reduction of Risk Factors for Cardiovascular Complications by BM 17.0744

Johannes Pill and Kirstin Meyer

Therapeutics Research, Roche Diagnostics GmbH, Mannheim, Germany

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INTRODUCTION

Vascular complications are the major cause of death in patients with type 2 diabetes (33,42,47), which is often associated with obesity, hypertension, dyslipidemia, and other abnormalities of metabolism. In 1988, Reaven (39) called this cluster of disorders “Syndrome X”, but it is also referred to as the metabolic syndrome or insulin resistance syndrome (16). These metabolic disorders lead to atherosclerotic lesions that cause an increased incidence of coronary heart disease (CHD), myocardial infarction, and angina (12). There is strong evidence in favor of a central role of insulin resistance and compensatory hyperinsulinemia in the genesis of every facet of the problem (4,9).

Insulin resistance is defined as the loss of sensitivity in the peripheral and hepatic tissue to insulin-mediated glucose uptake. Various pathogenetic mechanisms are reported to contribute to insulin resistance, for example, disturbances at different sites of the insulin receptor signal transduction pathway, cellular metabolism of fatty acids, adipose tissue distribution, and lifestyle—predominantly eating habits and lack of physical exercise (32). Hyperinsulinemia is the consequence of the decrease in the sensitivity of the target tissues to maintain glucose homeostasis. If enhanced secretion of insulin cannot maintain glucose homeostasis, type 2 diabetes becomes overt (15,24).

Insulin resistance with the attendant chronic hyperinsulinemia is often associated with various lipid abnormalities that are known risk factors for atherosclerosis and CHD (22,43). Increases in very low density lipoproteins (VLDLs) and triglycerides have been linked to insulin resistance via elevated circulating free fatty acids (FFAs), a characteristic feature of type 2 diabetes (17).

Current therapy of type 2 diabetes is directed at decreasing insulin resistance in the periphery by appropriate individual management of diet, physical exercise, and body weight (10). Additional pharmacotherapy is indicated if these means are insufficient with respect to glycemic control. Clinical trials demonstrate convincingly the impact of improved glycemic control on reduction of late complications (8,45). Oral therapies have focused on stimulation of insulin secretion by sulfonylureas and other insulin secreta-
Biguanides act by stimulation of aerobic glycolysis and inhibition of gluconeogenesis. Amelioration of insulin resistance is also claimed (6). Inhibition of intestinal carbohydrate digestion via \( \alpha \)-glucosidase inhibition (acarbose, voglibose, miglitol) leads to retardation in its uptake (2). The antidiabetic agents mentioned above have no or only a modest impact on insulin resistance.

A new class of compounds, thiazolidinediones (TZDs), enhances insulin action or partially mimics its action on insulin-sensitive peripheral tissue. These insulin sensitizers act at the nuclear level by stimulating peroxisome proliferator-activated receptor \( \gamma \) (PPAR\( \gamma \)), leading to enhanced synthesis of insulin-responsive proteins. Hence, as some of these genes are controlled by insulin, TZDs may amplify or mimic insulin genomic effects (7). PPAR\( \gamma \) is highly expressed in adipose tissue. Increases in lipoprotein lipase and fatty acid transport protein may explain the lipid-lowering properties and may essentially contribute to a reduction in insulin resistance. An increase in glucose transport (5,13) in adipose tissue and muscle, as well as an increase in glycogen synthesis and decrease in gluconeogenesis (5), has been demonstrated for TZDs. There is also evidence that TZDs act directly on the insulin signal transduction pathway (21,26,51). Antidiabetic effects of TZDs were observed only in some type 2 diabetics known as “responders.” This is in line with the heterogeneity of the pathophysiology of type 2 diabetes and indicates the need for agents that reduce resistance to insulin by another mode of action. Most clinical experience has been gained in this class of TZD compounds with troglitazone. Amelioration of hyperglycemia, hyperinsulinemia, and hypertriglyceridemia has been shown. High-density lipoproteins (HDLs) were increased, and HbA\(_{1c}\) as well as blood pressure were lowered in treated patients (31). Reduced insulin resistance was confirmed by glucose clamp studies (18).

Hepatotoxicity was found to be the main clinical concern with troglitazone. Besides abnormal liver function, obvious predisposing features are not known (14,30,50). If susceptibility to hepatotoxicity depends mainly on abnormal liver status, better tolerability may be more likely using more potent TZDs at lower dosages. Pioglitazone, rosiglitazone, and darglitazone, highly potent TZDs, are in different stages of clinical development. Postmarketing clinical studies will be needed to provide an answer on possibly reduced hepatotoxicity because of the low incidence of the problem.

Certain \( \omega \)-substituted alkyl carboxylic acids with the general formula “ring-spacer-COOH” were found to increase insulin-stimulated \([^{14}\text{C}]\)acetate incorporation into triglycerides in hepatocytes (29) or glucose consumption in adipocytes \textit{in vitro} (37). This may indicate an improvement in insulin action. In animal models of type 2 diabetes, hyperglycemia and hyperinsulinemia were reduced in parallel. This offers the hope of an improvement in insulin sensitivity by the drugs. BM 17.0744 was selected from this group of compounds because of its superior pharmacodynamic, pharmacokinetic, and toxicological properties.

**CHEMISTRY**

Chemical Structure of BM 17.0744

\[
\text{Cl} \quad \text{(CH}_2\text{)}_{10}\text{-CCl}_2\text{COOH}
\]

\((2,2\text{-Dichloro-12-}(p\text{-chlorophenyl})\text{dodecanoic Acid})\)
The drug was prepared in a straightforward manner by alkylation of the dianion of dichloroacetic acid with 1-bromo-10-(p-chlorophenyl)dodecane at 37°C in tetrahydrofuran. The required alkylbromide was obtained directly from 1,10-dibromodecane by Tsuji-Schlosser coupling with 4-chlorophenylmagnesium-bromide (29).

**PHARMACOLOGICAL STUDIES**

**Insulin Potentiating Activity in Vitro**

Enhancement of the synthesis of fatty acids in the liver is one of the insulin-mediated processes of cellular metabolism (19). The incorporation of radiolabeled precursors in end products of biosynthetic pathways is an appropriate method to study the effects of xenobiotics in various types of cells (41). BM 17.0744 and the insulin sensitizer, pioglitazone, were therefore investigated for their effects on insulin-stimulated [14C]acetate incorporation into triglycerides in primary rat hepatocyte monolayer cultures (34). *De novo* synthesized cholesterol was also measured. Both agents enhanced triglyceride synthesis significantly in the presence of insulin in concentrations of 25 milliunits/L and higher (Fig. 1). A pronounced reduction of cholesterol *de novo* synthesis was observed with BM 17.0744 only. This effect is independent of the insulin concentration in the incubation medium.

An increase in glucose uptake and metabolism is a further insulin-mediated process. Glucose consumption was measured in primary rat adipocytes obtained from abdominal fat pads of male Sprague-Dawley rats (Fig. 2). Insulin enhanced glucose consumption at a concentration higher than 10⁻⁹ mol. The maximum increase is about threefold higher than control values in the absence of insulin.

**FIG. 1.** Effects of BM 17.0744 and pioglitazone on [14C]acetate incorporation into triglycerides (A) and cholesterol (B) in primary rat liver monolayer cultures. Rat hepatocytes were incubated for 48 h in DMEM in the presence of [14C]acetate (37 Bq/mL), insulin (0 to 250 units/L), and the drugs (30 μmol) dissolved in DMSO (final concentration, 0.1%). The means ± S.E.M. of nine culture dishes from three independent preparations are given.
than that of insulin-free cultures. Both BM 17.0744 and the TZD troglitazone shifted the insulin concentration-response curve to the left. The maximum stimulation of glucose consumption by insulin is not affected, which indicates an increase of insulin sensitivity by the test compounds. The rates of aerobic glycolysis were determined by $[^{14}C]$CO$_2$ release from $[^{14}C]$glucose using isolated soleus muscle strips from genetically obese Zucker rats (13). Soleus muscle from obese Zucker rats exhibits insulin resistance, as is evident from decreased insulin-stimulated aerobic glycolysis compared with that in muscle from lean (fa/+) litter mates (0.32 ± 0.05 vs. 1.54 ± 0.17 μmol glucose/g/h). Whereas all compounds tested showed antidiabetic effects in animals (35), BM 17.0744 and troglitazone increased only $[^{14}C]$CO$_2$ release from $[^{14}C]$glucose (Fig. 3).

The in vitro data provide evidence of enhancement of the insulin action by BM 17.0744 in liver, adipose tissue, and muscle, three tissues important for the regulation of glucose homeostasis. An antidiabetic effect in animal models of type 2 diabetes can be expected. Reduced de novo synthesis of cholesterol could lead to cholesterol lowering in blood.

Antidiabetic and Lipid-lowering Effects of BM 17.0744 in Animal Models

Enhancement of insulin action should result in an improvement of the diabetic status in animal models for prediabetic status and type 2 diabetes. To broaden the in vivo relevance of the antidiabetic effect of BM 17.0744, investigations on diabetic status were performed in ob/ob, db/db, yellow KK mice, and fa/fa Zucker rats, animals with another genetic background of the disease (36), as well as in insulin-deficient rats and in metabolically healthy rats.

ob/ob Mice

In hyperglycemic ob/ob mice, lower blood glucose values were found in BM 17.0744-treated animals during the 24-h observation period, even after a single dose (Fig. 4). After the fourth administration, all blood glucose values were below those of control animals already in the group treated with the low dose of 0.3 mg/kg/d. In the groups treated with 1 and 3 mg/kg/d, nearly normal blood glucose values were observed during the 24-h observation period. The antihyperglycemic effects in ob/ob mice demonstrate the relevance of the in vitro observed insulin potentiation by BM 17.0744 for in vivo conditions.

db/db Mice

The db/db mice had a metabolic status characterized by high blood glucose and relatively low serum insulin (control group: 108 ± 4 microunits/mL), which is more a reflection of the situation in late stage type 2 diabetes in humans. Blood glucose, triglycerides, and FFAs were reduced in a dose-dependent manner by BM 17.0744 at the end of the treatment period of 5 d (Fig. 5). Hyperinsulinemia was unaffected under these conditions.

Yellow KK Mice

Troglitazone was given to the yellow KK mice to enable comparison with a therapeutically used insulin-sensitizing agent. Glucose and insulin in the blood of female yellow KK mice were lowered by BM 17.0744 as well as by troglitazone (Fig. 6). The maximum
The effect on both parameters was much more pronounced with BM 17.0744 and was achieved with significantly lower dosages compared with troglitazone.

**fa/fa Zucker Rats**

An animal model with high-grade insulin resistance is provided by obese *fa/fa* Zucker rats. Blood glucose is not or only moderately enhanced, which simulates the prediabetic state.

**FIG. 2.** Insulin-dependent glucose consumption in primary rat adipocyte cultures in HEPES buffer with glucose (1 mmol/L) and other additives in the absence and presence of BM 17.0744 and troglitazone dissolved in DMSO (final concentration, 0.1%). Glucose concentrations in incubation medium were measured after an incubation period of 3 h. The means of three independent cultures relative to solvent-treated drug and insulin-free cultures are given. (With permission from ref. 36).

**FIG. 3.** Effects of BM 17.0744, troglitazone, and BM 17.0249 (2,2,13,13-tetrachloro-tetradecane-1,14-dioic acid) on aerobic glycolysis in rat isolated soleus muscle. Isolated soleus muscle strips from male *fa/fa* Zucker rats were preincubated in Krebs-Ringer buffer containing 5.5 mmol/L of glucose for 30 min. Subsequently $[^{14}C]CO_2$ release from $[^{14}C]glucose$ was determined in the presence of the drugs in the indicated concentrations and 5 mmol/L of insulin (mean ± S.E.M., $n = 6$).
FIG. 4. Twenty-four-hour blood glucose profile in male ob/ob mice housed under a reversed dark/light cycle after the first (A) and fourth (B) oral dosing of BM 17.0744 in aqueous carmellose. The controls were treated with the same amount of vehicle (mean ± S.E.M., n = 10). (With permission from ref. 36).

 FIG. 5. Blood glucose, triglycerides (TG), and free fatty acids (FFAs) in the serum of male db/db mice 2 h after the fifth oral administration of BM 17.0744 in aqueous carmellose. The controls were treated with vehicle only (mean ± S.E.M., n = 10; Mann-Whitney test: ***P ≤ 0.01). (With permission from ref. 36).
status or onset of type 2 diabetes. A dose-dependent reduction of serum insulin was found under starved conditions and under conditions of the oral glucose tolerance test (OGGT) after 28 d of oral administration of BM 17.0744 (Fig. 7). FFAs were lowered in the middle and high dose groups (Fig. 8). High doses of bezafibrate also reduced hyperinsulinemia, but to a lower degree. The decrease in FFAs was greatest with this agent. Time courses of blood glucose in the OGGT were comparable in all treated groups with that of the control. The same blood glucose levels with a lower blood insulin may indicate an increase in sensitivity to insulin. In addition to triglycerides, circulating FFAs are reported to contribute to insulin resistance in type 2 diabetes (17). The antihyperinsulinemic effect

**FIG. 6.** Blood glucose and serum insulin in female yellow KK mice 2 h after the eighth oral administration of BM 17.0744 and troglitazone in aqueous carmelllose. The controls were treated with vehicle only (mean ± S.E.M., n = 10; Mann-Whitney test: ★ P ≤ 0.05, ★★ P ≤ 0.01).
of bezafibrate may therefore be based predominantly on amelioration of lipid metabolism. The much weaker effect of BM 17.0744 on FFAs and the simultaneously greater reduction of hyperinsulinemia suggest other mechanisms than FFA lowering as the main cause of reduction of insulin resistance by BM 17.0744.

Glucose clamp studies under conditions of high insulin resistance are ideal to investigate its improvement. An euglycemic glucose clamp study was performed in obese male Zucker rats pretreated with BM 17.0744 (10 mg/kg/d) orally for 10 d (Fig. 9). Glucose infusion to maintain constant individual blood glucose values was required in controls

FIG. 7. Serum insulin in oral glucose tolerance test at day 28 in male obese fa/fa Zucker rats after oral administration of BM 17.0744 or bezafibrate in aqueous carmellose or vehicle alone for 28 d (mean ± S.E.M., n = 5 to 9).

FIG. 8. Free fatty acids (FFAs) in the serum of male obese fa/fa Zucker rats after oral administration of BM 17.0744 or bezafibrate in aqueous carmellose or vehicle alone for 28 d (mean ± S.E.M., n = 5 to 9; Mann-Whitney test: ★P ≤ 0.05, ★★P ≤ 0.01).
only when a priming dose of insulin of 9 milliunits/kg/min was infused. Drug-treated animals needed about three times more glucose in this period, and this persisted during administration of the maintenance dose of insulin also. The higher glucose infusion rate in BM 17.0744-pretreated rats is a strong indication of reduction of insulin resistance and supports the conclusion drawn from the data on the oral glucose tolerance test.

Streptozotocin Diabetic Rats

A single administration of streptozotocin (65 mg/kg, i.v.) resulted in male Sprague-Dawley rats in severe hyperglycemia 7 d after administration. BM 17.0744 at doses of 3 and 12 mg/kg/d did not show any effect during the treatment period of 5 d or up to 3 d
posttreatment (Table 1). The lack of any effect of BM 17.0744 in an insulin-deficient animal model strongly suggests that the presence of insulin is necessary for the pharmacological effect of the compound.

Taken together, the experiments in animal models of type 2 diabetes and insulin resistance demonstrate the antihyperglycemic and antihyperinsulinemic properties of BM 17.0744. The antidiabetic potency of the drug is independent of the species and sex of the animals or the genetic background of the disease. Reduction of insulin resistance, as suggested by simultaneous lowering of blood glucose and insulin and as demonstrated in a clamp study, is in line with enhancement of insulin action found in in vitro experiments.

Metabolically Healthy Rats

To verify that reduction of triglycerides and FFAs in diabetic and prediabetic animals is mediated by improvement of the diabetic status or an additional direct drug effect, metabolically healthy rats were given BM 17.0744 for 28 d. Serum cholesterol and triglycerides were reduced nearly maximally with the lowest administered dose of 1.5 mg/kg/d (Fig. 10). The extent of lipid lowering in rats is comparable with that of bezafibrate. Hypoglycemia was not observed with either compound. The data strongly indicate that lipid lowering is an additional action of BM 17.0744 that is independent of its antidiabetic potency.

Mode of Action

Lipid lowering by BM 17.0744 was associated with elevated carnitine acetyl transferase (CAT) activity in the livers of rats (36). Enhancement of CAT may be an indication of an increase in fatty acid catabolism. The effects of drug treatment on β-oxidation-related enzymes were therefore investigated in male and female Sprague-Dawley rats at doses of 45 mg/kg/d. An increase in β-oxidation is reported to be associated with elevation of liver and kidney weight in small rodents, a phenomenon known for other xenobiotics, for example, fibrates (49). Enzyme activities were therefore measured in the liver and the kidney (Figs. 11 and 12). Acyl-CoA oxidase (AOX) and catalase activities in the liver were enhanced to a comparable extent in both sexes. Slight changes in urate oxidase (UOX), esterase, and cytochrome c oxidase (CYT.C.OX.) indicate specificity of the increase in β-oxidation. The same response to treatment was found in the kidney, but at

| BM 17.0744 | 255 |

**TABLE 1.** Effects of BM 17.0744 on blood glucose in streptozotocin diabetic rats

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a lower level. UOX is not present in the kidney (46). All the values were found to be below the limit of detection.

Concomitantly with the dramatic increase in β-oxidation enzyme activities, a rise in the corresponding proteins could be demonstrated by immunoblotting for AOX, enoyl-CoA hydratase/3-hydroxy-acyl-CoA dehydrogenase (PH), and 3-ketoacyl-CoA thiolase (PT) and other β-oxidation enzymes (Fig. 13). Increased protein is related to higher levels of mRNA as shown by Northern dot blot analyses (Fig. 14). This suggests that BM 17.0744 differentially regulates genes that encode for β-oxidation enzymes.

Stimulation of fatty acid catabolism due to an enhancement in β-oxidation may explain the lipid lowering by BM 17.0744. The effect is part of a modulation of lipid metabolism at the cellular level by interference of the drug with a nuclear receptor known as peroxisome proliferator-activated receptor (PPAR) subtype α (28). This subtype of PPARs is thought to play an important role in lipid homeostasis and glucose metabolism (40,48).

FIG. 10. Serum triglycerides (TGs) and cholesterol (CH) in male Sprague-Dawley rats during oral administration of BM 17.0744 in aqueous sodium carmellose for 28 d (mean ± S.E.M., n = 6 to 8). (With permission from ref. 36).
Hypolipidemic drugs like fibrates, long-chain fatty acids, and arachidonic acid metabolites are also reported to activate PPARα (20). The increase in liver and kidney weights in rats could also be interpreted as a consequence of binding to PPARα because a high density of this receptor was found in these organs (3).

PHARMACOKINETICS

The pharmacokinetic profile of BM 17.0744 was investigated in species relevant to pharmacology and of potential interest in toxicology.
Serum drug concentrations were determined after a single administration of BM 17.0744. The pharmacokinetic parameters summarized in Table 2 show a short half-life for mice, rats, and monkeys, even in the case of high dosing. In contrast, a long half-life was found in male and female beagle dogs, which strongly indicates accumulation of BM 17.0744 in this species after multiple administrations.

With dosing taken into account, the comparability of the area under the concentration-time curve (AUC) after i.p. and p.o. administration suggests good bioavailability of the drug. Accumulation of BM 17.0744 in humans is less likely, because of the short half-life of the drug in most species tested, including monkeys.
BM 17.0744 was well tolerated in the pharmacological dose range in diabetic and healthy animals. At the end of a 4-w administration to healthy male Sprague-Dawley rats (Table 3), the body weight was reduced in the high dose group of 12.5 mg/kg/d. The transaminases GOT and GPT in serum were unchanged (data not given), whereas alkaline phosphatase (AP) was higher in the dose groups of 6 and 12.5 mg/kg/d. None of the organs showed any weight changes, apart from the liver and kidneys, which showed an increase. These effects were quantitatively comparable with those of bezafibrate (36).

Enhancement of these organ weights and an increase in AP, together with lipid lowering and induction of β-oxidation enzymes, are reported for other peroxisome proliferators, for example, fibrates (11,38,49). An excessive response was found in small rodents such as mice, rats, and hamsters (known as high responders) only and not in other species, including humans (1,25).

The much weaker induction of β-oxidation enzymes in the livers of dogs and guinea pigs after administration of BM 17.0744 (28) and the absence of an increase in liver and kidney weights is in line with the experience gained with fibrates. These results indicate that the dramatic changes in the liver and kidney observed in rats are not directly transferable to other species, including humans. The data suggest a toxicological profile for BM 17.0744 similar to that of the fibrates.

FIG. 13. Immunoblots of representative peroxisomal enzymes from livers of male and female Sprague-Dawley rats after oral administration of BM 17.0744 (45 mg/kg/d) in aqueous carmellose or vehicle alone for 28 d. The total protein applied was 10 μg for each lane. The blots were incubated with polyclonal, monospecific antibodies against acyl-CoA oxidase (AOX), 13-enoyl-CoA hydratase/β-hydroxyacyl-CoA dehydrogenase (PH), 3-ketoacyl-CoA thiolase (PT), catalase, and urate oxidase (UOX), followed by peroxidase-conjugated goat anti-rabbit-IgG as secondary antibody. Immune complexes were visualized by chemiluminescence.

TOXICOLOGY

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TABLE 2. Pharmacokinetics of BM 17.0744 in different animal species after single dosing

FIG. 14. Northern dot blots of representative peroxisomal enzymes from livers of male and female Sprague-Dawley rats after oral administration of BM 17.0744 (45 mg/kg/d) in aqueous carmellose or vehicle alone for 28 d. The total RNA applied was 0.5 μg for each dot. Blots were hybridized with digoxigenin-labeled probes of acyl-CoA oxidase (AOX), 13-enoyl-CoA hydratase-hydroxyacyl-CoA dehydrogenase (PH), 3-ketoacyl-CoA thiolase (PT), catalase, and urate oxidase (UOX). The membranes were incubated with anti-digoxigenin fab fragments and visualized by chemiluminescence.
A reduction in adipose mass and not a general retardation of development of body weight can be expected in the high dose group of 12.5 mg/kg/d, because all organ weights except those of the liver and kidney were in the normal range. This is in contrast to the insulin sensitizers of the TZD group that induce adipogenesis in rodents (44).

**TABLE 3. Effects of BM 17.0744 treatment in male Sprague-Dawley rats**

<table>
<thead>
<tr>
<th>Dose (mg/kg/d)</th>
<th>Body weight (g)</th>
<th>Liver weight (g)</th>
<th>Kidney weight (g)</th>
<th>AP in serum (units/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>312 ± 10</td>
<td>13.3 ± 0.4</td>
<td>2.36 ± 0.05</td>
<td>470 ± 33</td>
</tr>
<tr>
<td>1.5</td>
<td>310 ± 6</td>
<td>15.0 ± 0.6</td>
<td>2.57 ± 0.07</td>
<td>428 ± 29</td>
</tr>
<tr>
<td>3</td>
<td>288 ± 9</td>
<td>14.7 ± 0.5</td>
<td>2.44 ± 0.08</td>
<td>493 ± 49</td>
</tr>
<tr>
<td>6</td>
<td>284 ± 5</td>
<td>17.9 ± 0.8***</td>
<td>2.58 ± 0.08</td>
<td>686 ± 68**</td>
</tr>
<tr>
<td>12.5</td>
<td>259 ± 18*</td>
<td>19.4 ± 1.3***</td>
<td>2.66 ± 0.13</td>
<td>734 ± 58**</td>
</tr>
</tbody>
</table>

* Body, liver, and kidney weights, as well as alkaline phosphatase (AP) activity, were determined after oral administration of BM 17.0744 in aqueous sodium carmellose for 28 d (mean ± S.E.M., n = 6 to 8; Mann-Whitney test: * P ≤ 0.05, ** P ≤ 0.01). (With permission from ref. 36.)

A reduction in adipose mass and not a general retardation of development of body weight can be expected in the high dose group of 12.5 mg/kg/d, because all organ weights except those of the liver and kidney were in the normal range. This is in contrast to the insulin sensitizers of the TZD group that induce adipogenesis in rodents (44).

**FIG. 15.** Putative mechanism of action of BM 17.0744 and its expected impact on the therapy of metabolic disturbances. PPARα, a member of the family of nuclear hormone receptors, may mediate the action of BM 17.0744 in a ligand-specific and organ-selective manner. Activation leads to modulation of synthesis of the proteins relevant in the metabolic pathways indicated. This results in improvement of the cardiovascular risk factor profile. Interference of the different sites of improved metabolic situation (for clarity not indicated by arrows) may cause a further strengthening of therapeutic effects.
CONCLUSION AND PERSPECTIVES

BM 17.0744 is a structurally new insulin sensitizer with intense antihyperglycemic and antihyperinsulinemic potency. Its mechanism of action involves lowering of triglycerides and FFAs mediated by induction of catabolic enzymes at a nuclear level (Fig. 15).

Insulin resistance, the key feature in the pathophysiology of type 2 diabetes, is ameliorated in diabetic and prediabetic states. This gives hope that the onset of type 2 diabetes might be prevented.

A toxicological profile similar to that known from fibrates is to be expected. The worldwide therapeutic use of fibrates over about two decades as lipid-lowering and modulating agents indicated their relative safety. The potential risks with BM 17.0744 should be viewed in comparison with the structurally unrelated insulin sensitizers of the TZD family. These compounds can cause adipogenesis, plasma volume expansion, and an increase in heart weight as well as severe hepatotoxicity, which was observed only in humans.

The broad-spectrum effects of BM 17.0744 on disturbed metabolism make the substance of great interest for potential therapeutic use in treating symptoms of “Syndrome X.” The use of this drug is expected to significantly reduce the incidence of cardiovascular diseases.

REFERENCES


