Troglitazone – a novel antidiabetic drug for treating insulin resistance

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Troglitazone was discovered by Sankyo Co. Ltd, in 1982. It represents a new class of antidiabetic agents targeted at ameliorating insulin resistance in type 2 diabetes patients. It is unrelated both chemically and functionally to the sulfonylurea and biguanide classes of oral antidiabetic agents. Troglitazone was found to reverse insulin resistance by its ability to increase insulin-stimulated glucose utilization and reduce hepatic glucose production. It has also been suggested that troglitazone exerts its insulin-enhancing effects by interacting with peroxisome proliferation activated receptor γ (PPARγ) regulated gene transcription.

Impaired insulin action in type 2 diabetes is thought to lead to hyperglycemia, with both environmental and complex genetic factors playing key roles. Although the primary lesion in type 2 diabetes is unknown, a number of studies suggest that metabolic defects in the liver, skeletal muscle and fat, and pancreatic β cells contribute to the disease. These metabolic abnormalities are characterized by the overproduction of hepatic glucose, impaired insulin secretion and peripheral insulin resistance.

In the current pharmacological treatment of type 2 diabetes, sulfonylurea (SU) drugs have mainly been used as oral hypoglycemic drugs to stimulate endogenous insulin secretion from β cells. SU drugs, however, sometimes aggravate the disease by causing fatigue of the pancreatic β cells, which leads to reduced drug efficacy after long-term treatment. This class of drugs also leads to enhanced obesity arising from the stimulation of endogenous insulin secretion in obese type 2 diabetic patients, plus an increased incidence of SU-induced hypoglycemia.

In 1979, Ng and Bornstein reported that the hypoglycemic activity of the synthetic peptide fragment of human growth hormone (hGH_{1-15}) was insulin dependent but did not alter the circulating levels of plasma insulin in normal or diabetic animals[1]. They also demonstrated that this peptide enhanced insulin sensitivity during intravenous insulin tolerance tests in streptozotocin-treated diabetic rats. Their results showing the insulin-potentiating action of the synthetic peptide prompted us to shift our search focus to the development of antidiabetic drugs that could potentiate insulin action.

Since 1980, we have made a major effort to develop a potential pharmacological therapy for the treatment of insulin resistance in peripheral tissues and/or suppression of abnormal hepatic glucose production in type 2 diabetic patients. Such a drug would be expected to have fewer side-effects and retain long-term efficacy.

Discovery of troglitazone

The formation of lipid peroxides underlies the pathogenesis of several diseases such as atherosclerosis, diabetes mellitus, inflammation and related ailments. Although endogenous lipids may be oxidized nonenzymatically by peroxidation (Figure 1), living organisms utilize natural antioxidants such as α-tocopherol, ascorbic acid, β-carotene, glutathione and

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superoxide dismutase to protect themselves from peroxidation. Based on this knowledge, it seemed appropriate to develop therapeutic agents with antioxidant activity.

About 16 years ago, we designed hypolipidemic agents with antioxidant activity by coupling the side-chain of gemfibrozil, which was known to be a hypolipidemic agent, with a hindered phenol group of α-tocopherol (Figure 2). Some of the synthesized compounds had potent antioxidant and hypolipidemic activities, but almost all were hepatotoxic. As an alternative approach to our drug discovery efforts, we designed and synthesized benzoxathiole derivatives with the intention of targeting them as hypolipidemic agents. By modifying probucol, clofibrate, and other hypolipidemic compounds, we designed a substructure on the basis of three moieties (highlighted in Figure 3). This substructure was combined with an element of α-tocopherol to produce 5-hydroxy-1,3-benzoxathioles (Figure 3).

The hypolipidemic activity of 1,3-benzoxathiole, however, was not as potent as probucol. Moreover, the compound inhibited the formation and release of a slow-reacting substance of anaphylaxis (SRS-A) and 5-lipoxygenase.

Additional hypolipidemic and hypoglycemic agents with antioxidant activity were designed; these are shown in Figure 4. Gemfibrozil, AL294, and ciglitazone were known hypolipidemic agents. Therefore, the three highlighted moieties of these compounds (shown in Figure 4) were joined with antioxidant and lipid peroxide-lowering groups to produce compounds **1**, **2**, **3** and **4**.

In 1982, troglitazone was synthesized (compound **4**). In 1983, we found that troglitazone had very potent lipid peroxide-lowering activities and caused no adverse effects[2]. Compound **3** also had very good hypolipidemic activity, but caused hepatic enlargement in rats. Figure 5 shows the synthetic route to troglitazone. Acetylation of trimethylhydroquinone with acetyl chloride in the presence of a Lewis acid such as aluminum chloride followed by Fries rearrangement of the acetyl group gives 5-acetoxy-2-hydroxy-3,4,6-trimethylacetophenone. A chroman intermediate, 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)

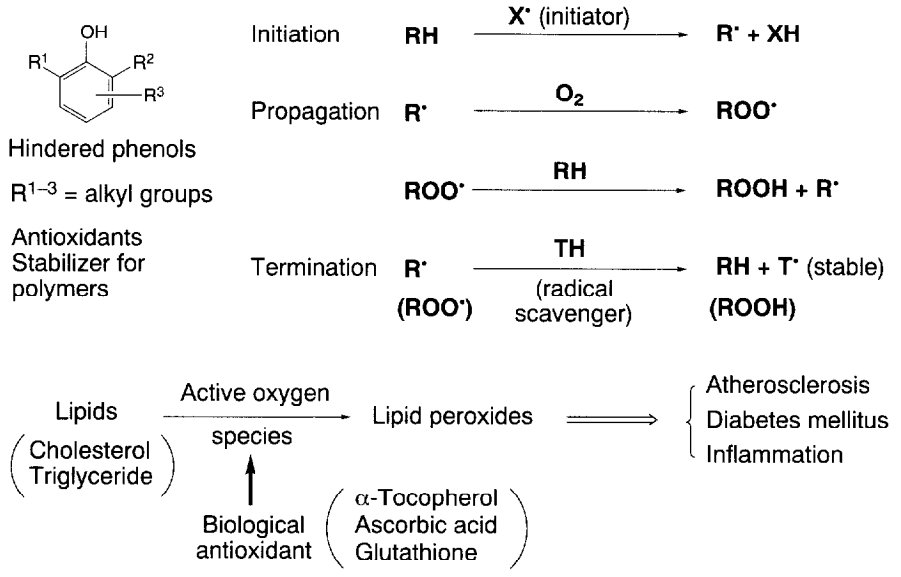

Figure 1. *Mechanism of antioxidant activity of hindered phenols for the peroxidation of organic compounds, and the possible role of hindered phenols as biological antioxidants for therapeutics.*

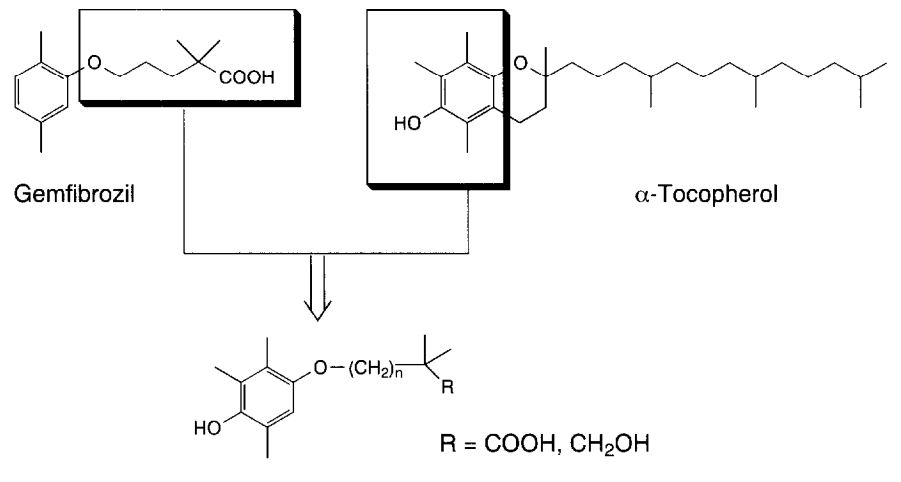

Figure 2. *Design of hypolipidemic agents with antioxidant activity.*

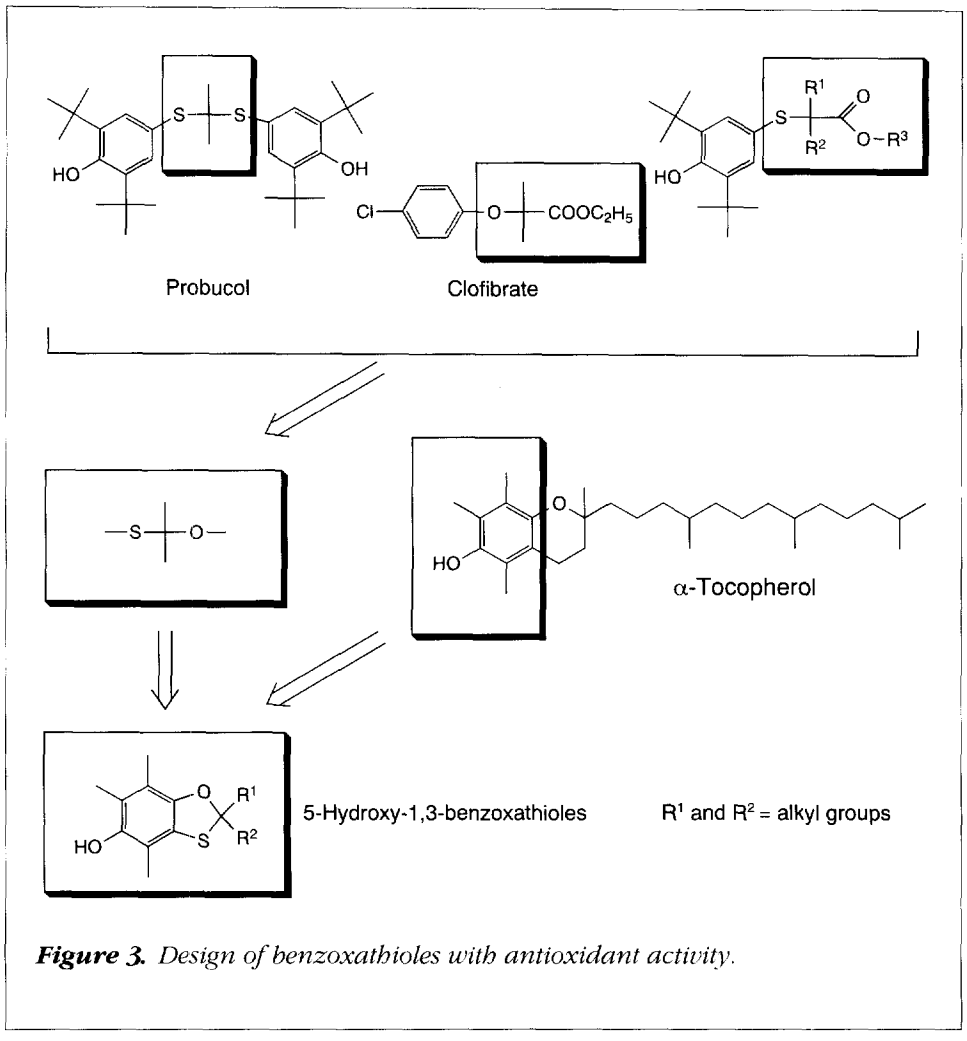

Figure 3. *Design of benzoxathioles with antioxidant activity.*

chroman-4-one (**6**), is formed by heating a mixture of the acetophenone and 4-nitrophenoxyacetone (**5**), which was prepared from 4-nitrophenol in the presence of pyrrolidine. Sodium borohydride reduction of the oxo compound (**6**) gives the corresponding hydroxy compound, which affords a chromene compound (**7**) by dehydration reaction of the hydroxy compound. Simultaneous catalytic reduction of the nitro group and hydrogenation of the double bond in the chromene (**7**) gives 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman (**8**). Diazotization of the amine (**8**) using hydrochloric acid or hydrobromic acid, followed by Meerwein arylation to butyl acrylate in the presence of a small amount of copper(I) oxide or copper(II) bromide, affords the corresponding 2-chloro- or 2-bromopropionate (**9**). Treatment of the halide (**9**) with thiourea on heating forms 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)-benzyl]-2-iminothiazolidin-4-one (**10**). Troglitazone (**4**) is prepared by hydrolysis of the imino compound (**10**)[3].

Pharmacological profile of troglitazone

Importance of animal studies

Animal models of disease are invaluable during the early phase of drug discovery. Therefore, in 1982, using KK mice as a genetically insulin-resistant model of type 2 diabetes, we initiated a series of related experiments to characterize and analyze the diabetic features observed during aging in KK mice. These spontaneously hyperglycemic animals are mildly obese, hyperglycemic and hyperinsulinemic and display polygenic inheritance. The development of hyperinsulinemia with hyperglycemia is most often attributed to the stress of obesity. Thus, both acquired and genetic factors are important to the initiation of diabetes in this model of type 2 diabetes.

Insulin sensitivity in KK mice, estimated by insulin tolerance test, was particularly impaired at 4–5 months of age, and we felt that this hyperinsulinemia reflected insulin resistance. Therefore, KK mice of 4–5 months of age were used in an *in vivo* assay that was designed to evaluate the hypoglycemic and hypoinsulinemic effects of our compounds[4]. If plasma glucose and plasma insulin levels were significantly decreased in these model animals, the drug might lead to increased insulin sensitivity.

To explore the hypoglycemic and hypoinsulinemic effects of our compounds *in vitro*, we established, in 1983, an insulin receptor binding assay as well as glucose uptake studies to further characterize insulin action in adipocytes from drug-treated animals. We tested many compounds and found, at the end of 1983, that troglitazone was the first example consisting of a thiazolidinedione ring and a chroman ring structure of vitamin E that could improve hyperglycemia, hyperinsulinemia and hypertriglyceridemia in diabetic KK mice.

Troglitazone also increased glucose uptake in drug-treated adipocytes[4]. These findings suggested that troglitazone increased not only insulin sensitivity but also insulin

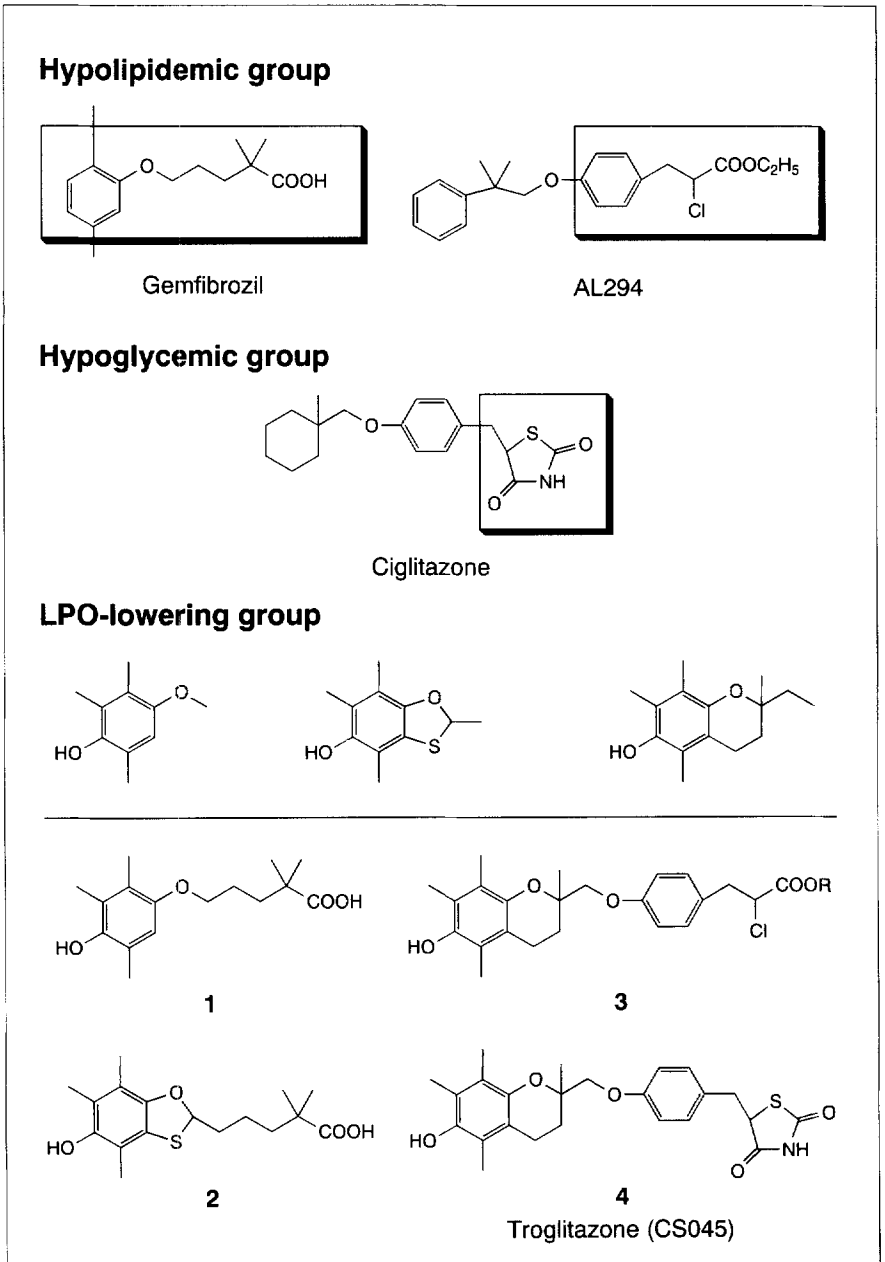

Figure 4. *Design of hypolipidemic and hypoglycemic agents with antioxidant activity. Compounds* ***1–4*** *were designed by combination of the highlighted moieties of hypolipidemic and hypoglycemic compounds and lipid peroxide (LPO)-lowering groups shown in the top panel.*

responsiveness. Finally, troglitazone {(±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)benzyl]-2,4-thiazolidinedione}, formally known as CS045, was selected as a potential antidiabetic agent after intensive testing.

Hypoglycemic actions in diabetic rats and mice

The pharmacological profile of troglitazone was assessed by means of several genetic and acquired animal models of type 2 diabetes with insulin resistance, including obesity, hyperglycemia, hyperinsulinemia and hypertriglyceridemia. Troglitazone significantly decreased both plasma glucose and insulin levels in several species of genetically insulin-resistant animal models of type 2 diabetes, such as KK, *ob/ob*, and *db/db* mice, and ZDF rats. Troglitazone also decreased plasma lactate, triglycerides, free fatty acids and ketone bodies[5].

It is thought that a reduction in a gluconeogenic substrate, such as lactate, reduces hepatic glucose production and that a reduction in free fatty acids and ketone bodies improves the aggravated effects that these metabolites recessively exert on peripheral glucose uptake. Food intake and body weight remained stable with troglitazone treatment in these diabetic animal models.

Similar results were obtained in other genetically obese Zucker fatty rats and in nongenetic models of insulin resistance – high-fructose-fed rats[5,6]. Plasma glucose, insulin and lipids were observed in these animals. Impaired glucose tolerance was essentially normalized in Zucker fatty rats treated with troglitazone, decreasing markedly both postprandial glucose and insulin levels after oral glucose load. Interestingly, troglitazone also prevented the induction of diabetes by dexamethasone in female Zucker rats (T. Fujiwara and H. Horikoshi, unpublished).

In contrast, troglitazone did not significantly improve hyperglycemia in streptozotocin-treated rats – a model of type 1 diabetes. Insulin tolerance tests, however, showed that treatment with troglitazone significantly improved insulin sensitivity. Moreover, combined treatment with troglitazone potentiated the hypoglycemic action of exogenous insulin and lowered the insulin dose to achieve an appropriate plasma glucose level[7].

Islet studies

Impaired islet cell function is a characteristic feature of type 2 diabetes. Pancreatic functions, such as islet morphology,

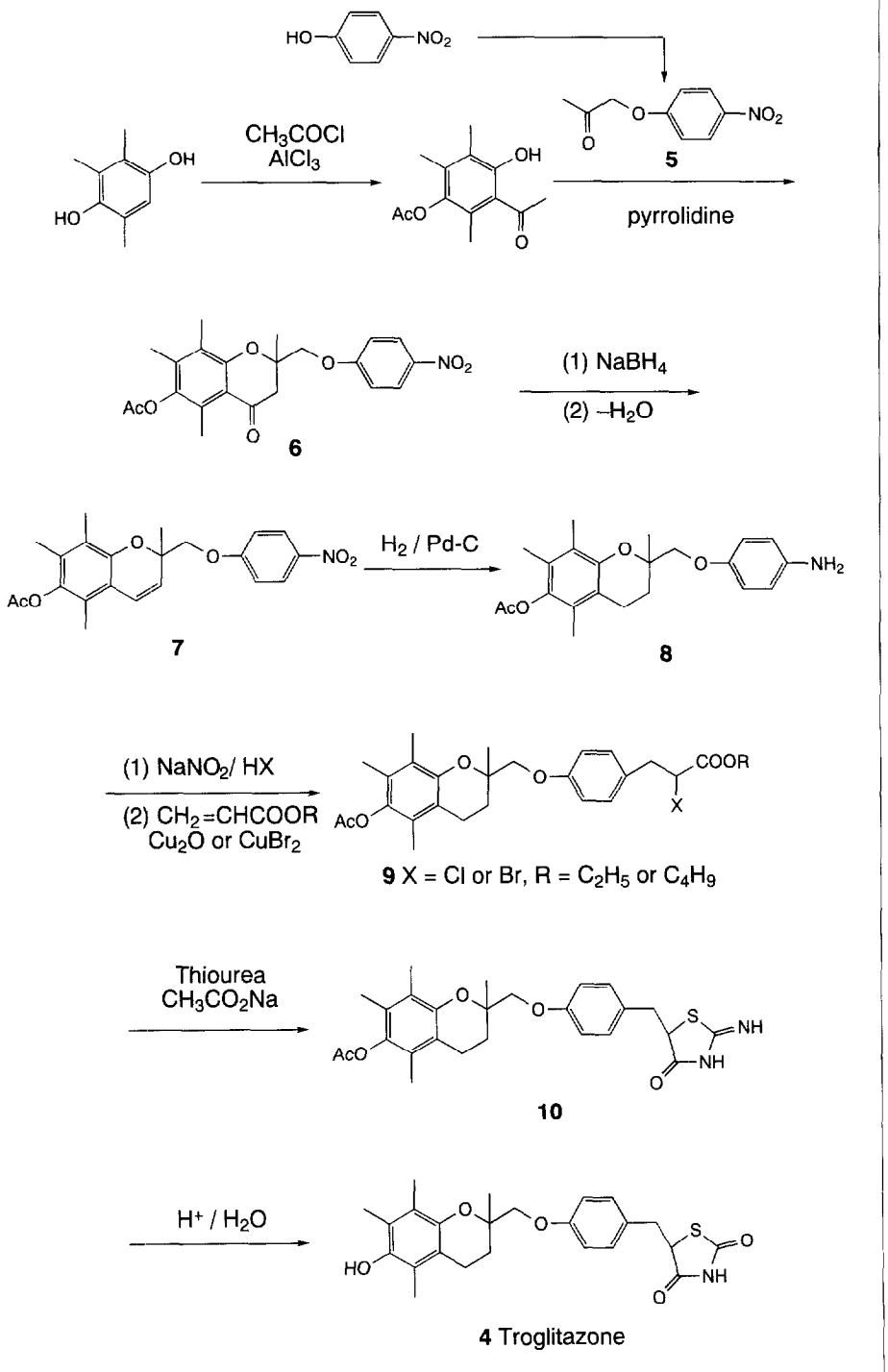

Figure 5. *Chemical synthesis of troglitazone.*

insulin content and glucagon content were examined in *db/db* and KK diabetic mice at early and late stages of diabetes. In both models, chronic treatment with troglitazone increased regranulation of islet β cells and the insulin content in the pancreas, as shown in Figure 6 (Refs 8,9). Furthermore, the direct effect of troglitazone on insulin secretion was assessed by a pancreatic perfusion system. However, troglitazone alone did not stimulate insulin secretion[10].

Hepatic glucose production

Abnormal elevation of hepatic glucose production resulting from increased gluconeogenesis is a major cause of fasting hyperglycemia in type 2 diabetes. We therefore analyzed gluconeogenesis in diabetic KK mice treated with troglitazone and found that gluconeogenesis is markedly elevated compared with nondiabetic control mice. Troglitazone reduced the rates of gluconeogenesis in diabetic mice but had no effect in normal mice[11].

We then determined the enzymatic step at which troglitazone influences the glycolytic/gluconeogenic pathway. The levels of the glycolytic intermediates were measured in liver of control and troglitazone-treated *db/db* and KK mice and subjected to crossover analysis. A crossover point was observed between fructose 6-phosphate and fructose 1,6-bisphosphate (FBP)[12]. These data suggested that troglitazone affects the interconversion of the two intermediates. Drug treatment led to a significant decrease in FBPase activity, without affecting phosphofructokinase activity. Concentrations of FBP remained unchanged with treatment. Overall, these data suggest that the reduced gluconeogenesis may result from a decrease in FBPase protein.

Glucose utilization

The acute effects of troglitazone on insulin-stimulated glucose utilization were observed in a hind-limb perfusion model[13]. This isolated perfusion system maintains muscle integrity and insulin responsiveness and allows for the

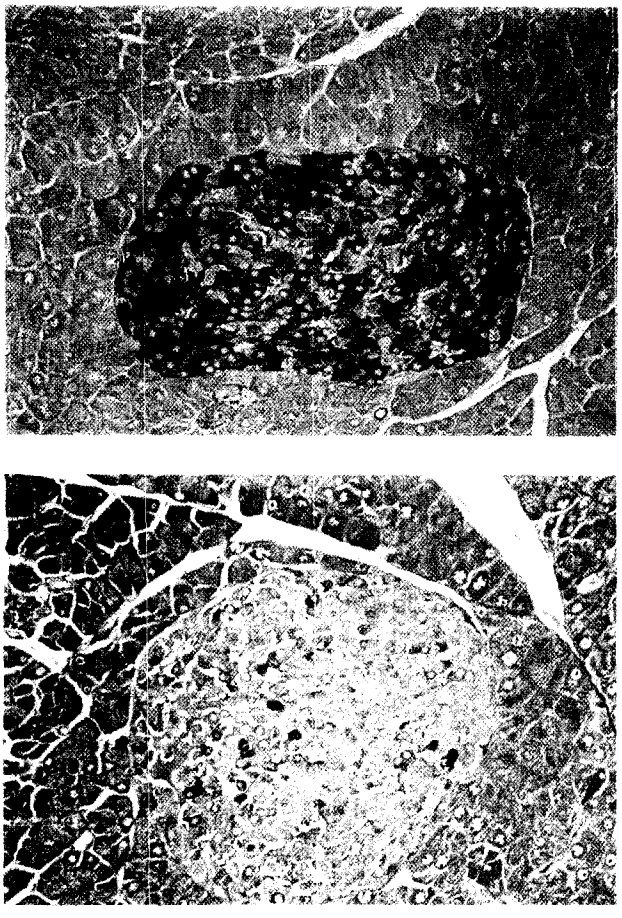

Figure 6. *Histology of pancreas before (a) and after (b) administration of troglitazone in KK mice.*

evaluation of glucose metabolism free from the influence of changes in endogenous hormones and metabolic feedback loops.

Insulin alone significantly increased glucose uptake, and insulin in combination with troglitazone further increased glucose uptake. The production of lactate and pyruvate as well as oxygen consumption were similar to the results observed for glucose uptake during the perfusion period. These acute effects of troglitazone were also confirmed on glucose disposal by a hyperinsulinemic, euglycemic clamp assay in normal SD rats[14]. In this system, troglitazone increased the overall rate of glucose disposal *in vivo*.

Adipose tissue is one of the major targets that is highly responsive to insulin. We decided to determine whether troglitazone affected adipose cell function. 2-Deoxyglucose uptake by insulin was evaluated in isolated adipocytes from treated and untreated animals[15]. Insulin produced a dose-dependent increase in 2-deoxyglucose uptake in adipocytes from both groups of animals. Troglitazone treatment significantly enhanced basal glucose uptake and shifted the insulin dose–response curve to the left. To explore the effect of troglitazone in cultured cells, L6 myocytes were chronically exposed to troglitazone[15]. Basal glucose uptake was significantly increased. Increases in Glut 1 transporter content and a small but significant increase in Glut 4 transporter levels were also observed.

Insulin promotes the formation of glycogen from glucose. The effect of troglitazone on the activity of glycogen synthase was studied in both HepG2 and BC3H-1 cells[16]. Treatment of both cell types with troglitazone produced a dose-dependent increase in glycogen synthase activity.

In summary, troglitazone appears to directly improve the action of insulin in liver, skeletal muscle and adipose tissues. It increases glucose disposal rates, and decreases hepatic glucose output. The metabolic mode of action of troglitazone is summarized in Figure 7.

Mechanism of action

A number of studies have suggested that thiazolidinediones exert their primary insulin-potentiating effects through the regulation of transcription[17–20]. This has been examined in cultured adipocytes. Addition of troglitazone to 3T3-L1 preadipocytes increased both the differentiation rate as well as the percentage proliferation[21,22]. However, it did not significantly influence the stimulation of mitogenesis by insulin or serum in 3T3-L1 fibroblasts. The transcription factor C/EBPα is necessary and sufficient for the conversion of preadipocytes to adipocytes. Troglitazone treatment increased the rate of accumulation of C/EBPα, but did not affect the mRNA levels of C/EBPα after differentiation was complete.

It has been demonstrated that thiazolidinediones induce adipocyte differentiation by interacting with members of the PPAR (peroxisome proliferation activated receptor) family. In combination with other C/EBP family members, these nuclear receptors are believed to induce synthesis of C/EBPα and thus promote adipocyte differentiation. Thiazolidinediones can serve as ligands for PPARγ (Ref. 18), a PPAR family member highly expressed in adipose tissue but also found in other tissues. PPAR activation thus initiates the cascade of transcriptional events which culminate in the expression of C/EBPα and adipocyte differentiation. The apparent mechanism of action of the thiazolidinediones like troglitazone involves binding to nuclear receptors that regulate gene expression. Figure 8 depicts hypothetical cellular

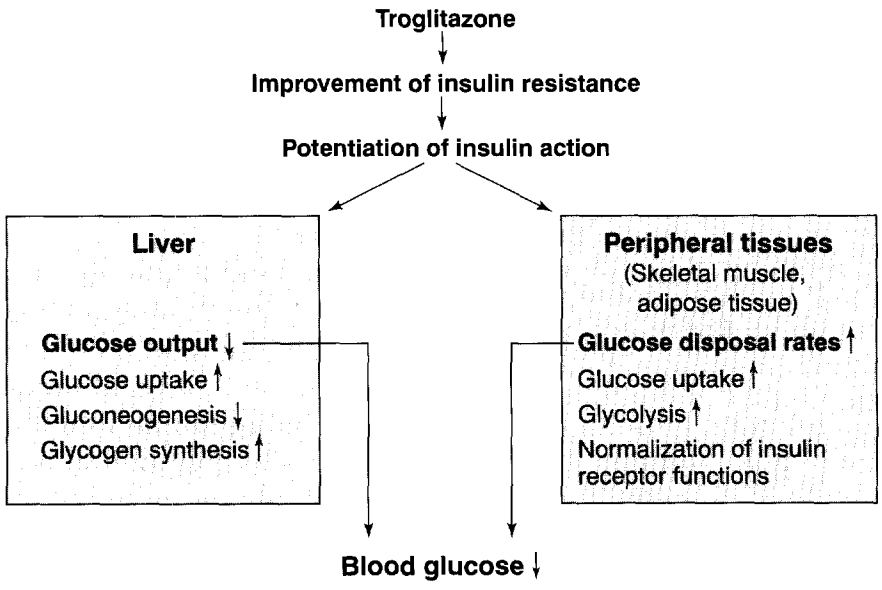

Figure 7. *Mode of action of troglitazone.*

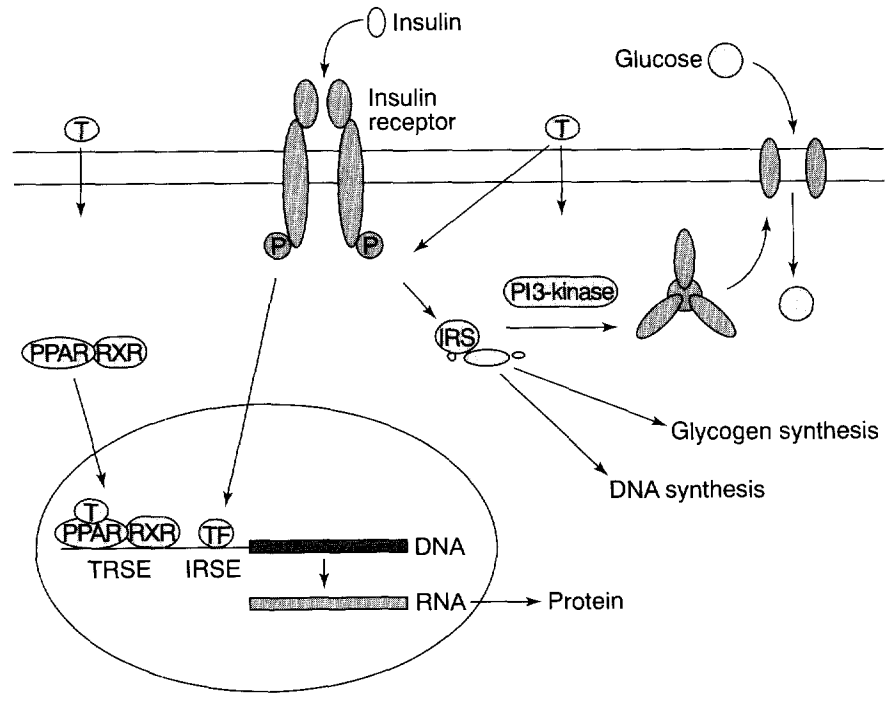

Figure 8. *Hypothetical model for the mechanism of enhancement of insulin action by troglitazone. IRSE, insulin response sequences; PPAR, peroxisome proliferator activated receptor; RXR, retinoid X receptor; T, troglitazone; TF, insulin-regulated transcription factors; TRSE, specific DNA sequences in thiazolidinedione responsive element.*

mechanisms by which troglitazone might act via transcriptional regulation. Troglitazone may interact with PPARγ. PPAR exists in a heterodimer with another nuclear receptor RXR (retinoid X receptor). The binding of troglitazone to PPARγ can induce the interaction of the complex with specific DNA sequences in thiazolidinedione responsive gene. This DNA binding may involve the displacement of a corepressor molecule on ligand binding.

Data now suggest that the modulation of PPARγ by troglitazone plays a critical role in regulating intermediary metabolism, although the full spectrum of genes that respond to this drug, either directly or indirectly, awaits further characterization.

Preclinical and clinical studies

At the beginning of 1984, we began to conduct various preclinical studies with troglitazone.

Toxicology

The toxicologic profiles of troglitazone were evaluated in mice, rats, dogs and monkeys. In rodents and monkeys, reversible reductions in red blood cell parameters were seen with evidence of increases in plasma volume, but they were not associated with significant effects upon hemopoiesis. These observations have been confirmed in healthy subjects[23]. Troglitazone 200 mg or 600 mg taken once daily for 6 weeks did not result in any clinically or statistically significant changes in red blood cell mass or other erythropoietic parameters. In addition, in rodents, reversible cardiac enlargement was observed and was not associated with histopathological adverse effects after 52 weeks of exposure to troglitazone levels 14 times

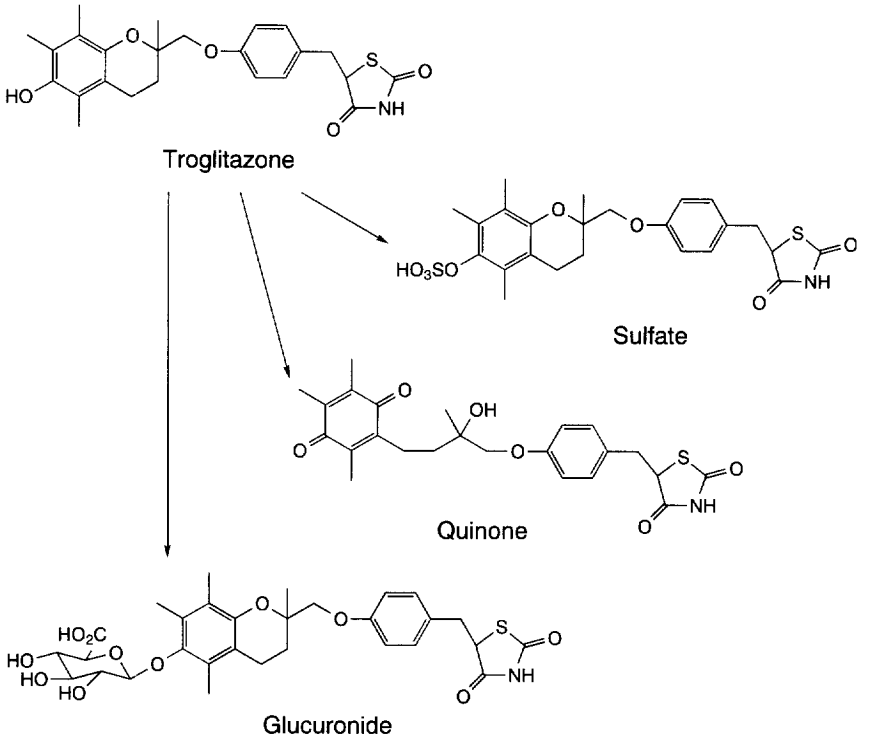

Figure 9. *Predicted metabolic pathway of troglitazone.*

the clinical therapeutic level. There were no significant changes in cardiac function in troglitazone-treated diabetic rats, and cardiovascular function appeared to improve[24]. Indeed, no adverse cardiac events or changes in left ventricular mass were observed in long-term clinical trials at doses up to 800 mg, and stroke volume and other measures of cardiac output improved[25]. General pharmacological studies showed no clinically significant problems[7].

Based on these and other toxicity studies, it was verified that troglitazone had no significant safety problem.

Pharmacokinetics

In 1985, a labeled compound was synthesized to examine absorption, distribution, metabolism and excretion of troglitazone in animals. Results revealed that troglitazone was rapidly absorbed after oral administration, distributed to the target organs, and then metabolized to conjugates in the liver, most of which were excreted in the feces (Figure 9)[7]. Linear kinetics for maximum plasma concentrations and the area under curve over the 200–600 mg daily dose range were observed in human subjects. Steady-state plasma concentrations were reached within 3–5 days of daily drug administration. Food increases the bioavailability of troglitazone by 30–85%. Troglitazone is extensively bound to serum albumin.

From these basic studies, it was determined that troglitazone was a promising new antidiabetic drug with a wide safety margin.

Clinical results

Clinical trials were conducted in Japan from 1987 to 1993 (Refs 26–31). Troglitazone was first licensed to Warner-Lambert for co-development and co-marketing with Sankyo in North America in 1991. It was also licensed to Glaxo-Wellcome in Europe in 1992. Based on our world-wide development program, clinical trials were conducted in North America from 1991 to 1996 (Refs 32,33) and in Europe from 1992 to 1997 (Ref. 34).

In these clinical trials, significant reductions in HbA_{1c} have been observed after 12 or 16 weeks of troglitazone (200–800 mg) compared with placebo[34]. Fasting blood glucose was reduced by ~20% relative to placebo. Fasting plasma insulin reductions of 10–34% compared with placebo were seen. At doses of 600 mg, reductions in triglycerides (20%) and free fatty acids (26%) were seen, as well as increases in high-density lipoprotein cholesterol (12%), compared with placebo. Troglitazone can be used as monotherapy in type 2 diabetic patients whose glycemic control is inadequate by diet alone or by oral hypoglycemic agents.

Approximately 50% of the improvement in glycemic control is seen within 2 weeks of initiating therapy; the full therapeutic effects may take 6–8 weeks. In contrast, hyperglycemia was improved within 1–2 days of initializing treatment with troglitazone, and troglitazone achieved maximum efficacy within a week. Compared with human data, these considerable time lags to obtain full efficacy may be caused by differences in metabolic turnover rates; however, this remains to be clarified.

Studies have been conducted on the combination of troglitazone with SUs in type 2 diabetic patients who are not adequately controlled by SU therapy. In the USA, type 2 diabetics were treated for 1 year with troglitazone (200, 400, 600 mg) in combination with 20 mg glybenclamide[25].

Reductions of HbA_{1c} levels were 1.60–2.65% mean change from baseline. This demonstrated the efficacy of troglitazone in combination with a SU. Efficacy of troglitazone in combination with SU was also confirmed in Japan[29] and Europe[35].

A combination of troglitazone with metformin has recently been investigated in type 2 diabetic patients who were initially treated with troglitazone 400 mg daily or metformin 2 g daily for 3 months[36]. The effects of the two agents on glucose control were comparable. After 3 months of combined troglitazone and metformin, both groups decreased their glucose levels by the same extent. These data suggest that the combination of troglitazone and metformin might lead to additive and potentially synergistic effects on glycemic control.

As troglitazone increases insulin sensitivity, troglitazone in combination with insulin should provide improved glycemic control and reduction in the use of insulin. Troglitazone (placebo, 200 or 600 mg) was added to a fixed dose of insulin. Clinically significant reductions in HbA_{1c} (11% to below 8%) were seen at 6 months of treatment[37].

The use of troglitazone in reducing exogenous insulin dosage while improving glycemic control was examined in a 6-month study. Patients treated with troglitazone 200 and 400 mg had their insulin doses decreased by 41% and 58%, respectively. Thus, troglitazone in combination with insulin potentially leads to a reduction in exogenous insulin dosage in insulin-dependent type 2 diabetic patients.

In summary, troglitazone appears to be an excellent agent when used in combination with SU, metformin or insulin for optimizing glucose control in type 2 diabetic patients.

No difference in safety was found between troglitazone and placebo groups in these clinical trials.

Based on the results of the preclinical and clinical studies, troglitazone is expected to be a clinically useful hypoglycemic drug in type 2 diabetic patients with insulin resistance who are inadequately responding to diet or SU drug or insulin therapy.

New avenues for troglitazone treatment

It has been widely recognized that insulin resistance and associated diseases are closely related by a set of metabolic abnormalities known as insulin-resistance syndrome[38]. This syndrome is manifested by compensatory hyperinsulinemia, including impaired glucose tolerance (IGT), polycystic ovarian syndrome (PCOS), dyslipidemia, vascular diseases, central obesity and hypertension. Any of these symptoms represents a major risk factor for coronary artery disease. Troglitazone is being studied in several of these human disease states.

Hypertension

Chronic troglitazone treatment of Zucker fatty rats and high-fructose-fed rats, both of which are useful animal models for mild hypertension associated with obesity and insulin resistance, could significantly improve mild hypertension and hyperinsulinemia[14,39]. If so, troglitazone may provide a new pharmacological approach to the management of hypertension in obese and/or type 2 diabetic patients with insulin resistance.

Atherogenesis

It has been suggested that lipid peroxide may play an important role in atherogenesis. Troglitazone is a bifunctional drug that can enhance insulin action and also potently inhibit lipid peroxidation[2]. As antioxidants reduce lipid peroxidation, they contribute to the decreased formation of plaque-forming foam cells. Troglitazone strongly inhibited low-density lipoprotein (LDL) peroxidation compared with α-tocopherol[40]. In addition, troglitazone strongly inhibited $CuSO_4$-induced oxidation of LDL (Ref. 41). On the basis of these data, it appears that troglitazone can considerably reduce atherogenic factors.

Impaired glucose tolerance

An initial study has been conducted in which obese patients with or without IGT were treated with troglitazone for 3 months[42]. The metabolic abnormalities associated with insulin resistance syndrome were strikingly corrected with troglitazone. The National Institutes of Health have initiated a large-scale, multicenter study, the Diabetes Prevention Program, which includes troglitazone as one of the treatment arms in IGT patients with insulin resistance. This study will attempt to determine whether conversion of high-risk individuals to diabetes can be prevented.

Polycystic ovarian syndrome (PCOS)

PCOS is another interesting disease state caused by insulin resistance. This syndrome is characterized by chronic anovulation and hyperandrogenism, which is considered one of the features in insulin resistance states. Hyperinsulinemia is also common in this syndrome. A recent clinical study found that troglitazone improved total body insulin action in PCOS by lowering plasma insulin

levels, and that it also concomitantly reduced elevated testosterone and luteinizing hormone levels towards the normal range[43].

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