pancreas is unable to sustain compensatory hyperinsulinaemia. Because the development of NIDDM is largely dependent on the coexistence of both defects, therapeutic strategies that serve either to enhance insulin secretion (that is, to maintain hyperinsulinaemia) or improve target tissue insulin sensitivity would be expected to prevent the progression of insulin resistance to glucose intolerance and NIDDM. Hyperinsulinaemia *per se* is, however, also linked to several metabolic abnormalities, which include insulin resistance, hypertriglyceridaemia, reduced plasma concentrations of high density lipoproteins and increased plasma concentrations of low density lipoproteins[1,7,9]. The association of insulin resistance and hyperinsulinaemia with these metabolic disorders has been termed 'Syndrome X' and is strongly linked to an increased risk of hypertension and coronary artery disease (CAD) (Refs 1,7,10); CAD is, indeed, a major cause of morbidity and mortality in NIDDM patients.

The therapy of glucose intolerance and NIDDM over the last 30 years has largely been directed towards improving glycaemic control by dietary and exercise regimes, and pharmacologically by use of sulphonylureas to enhance glucose-stimulated insulin secretion, biguanidines to suppress hepatic glucose output, or, more recently, by use of acarabose to inhibit carbohydrate absorption from the gut. The mechanism of action and clinical utility of these agents has been well reviewed[10–12] and will not be discussed in detail here. Sulphonylureas and biguanidines have been reported to improve insulin sensitivity, and their administration to patients with NIDDM results in improved insulin-induced whole-body utilization of glucose[10]. The improvement in insulin sensitivity as a result of administration of sulphonylureas is almost certainly secondary to the improved control of blood glucose concentrations that results from stimulation of the release of insulin from the β-cell. The mechanism of action of the biguanidines remains unclear, but effects on glucose absorption, hepatic glucose output and glucose utilization have been suggested[10]. The biguanidine metformin, the subject of a recent review[13], reduces elevated blood glucose levels without stimulating insulin secretion and reduces blood glucose only in the presence of hyperglycaemia[13–15]. The effects of metformin on peripheral glucose utilization in patients with NIDDM remains unclear; some studies show no effect but other workers report an improvement in glucose uptake[13]. The most recent study[15] indicates, however, that metformin reduces fasting blood glucose concentrations primarily by suppressing gluconeogenesis and thus reducing hepatic glucose output; this is in broad agreement with previous literature. Any method of reducing hyperglycaemia, however, would be expected to have some beneficial effect on glucose utilization as a result of amelioration of the deleterious effects of chronic hyperglycaemia on insulin sensitivity and impaired insulin secretion.

This article reviews recent advances in the discovery, development and understanding of the mechanism of action of thiazolidinedione insulin-sensitizing agents and the thermogenic and antidiabetic β_3-adrenoceptor agonists, two categories of compound that improve insulin resistance and are expected to progress to use in the clinical treatment of NIDDM.

Box 1. Putative molecular mechanisms of insulin resistance and NIDDM

Impaired insulin receptor autophosphorylation
Reduced insulin receptor tyrosine kinase activity
Reduced insulin receptor substrate-1 phosphorylation
Reduced phosphatidylinositol 3-kinase activity
Reduced cytosolic glucose transporter (GLUT 4) expression
Impaired translocation of GLUT 4 to the plasma membrane
Insulin receptor downregulation
Pancreatic GLUT 2 downregulation
Mutations of the pancreatic glucokinase gene
Insulin receptor mutations

Thiazolidinediones

The thiazolidinedione class of antihyperglycaemic agents may prove to be the most significant advance in the treatment of NIDDM since the advent of the sulphonylureas in the 1950s. In 1982 Sohda and coworkers[16], of Takeda, Inc., reported a novel class of glucose-lowering agents, the 5-substituted 2,4-thiazolidinediones. In this and other studies[17], they showed that in animal models of NIDDM, the archetypal compound ciglitazone (5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidinine-2,4-dione) suppressed hyperinsulinaemia, increased glucose tolerance and improved overall insulin sensitivity by reducing peripheral insulin resistance. Since then, several thiazolidinediones have been reported (Figure 1), of which pioglitazone[18] (Takeda/Upjohn), englitazone[19] (Pfizer), troglitazone[20] (Sankyo/Warner Lambert/Glaxo) and BRL 49653 (Ref. 21) (SmithKline Beecham) have been, or are, in clinical development.

In animal studies, thiazolidinediones reduce circulating insulin concentrations in hyperinsulinaemic, insulin-resistant animals; in hyperglycaemic insulin-resistant animals they also normalize plasma glucose concentrations[22,23]. They enhance

insulin-mediated suppression of hepatic glucose output, insulin-stimulated uptake and utilization of glucose by adipose tissue and skeletal muscle, and reduce levels of triglycerides and nonesterified free fatty acids in plasma[24]. In clinical studies, troglitazone (CS-045) has been shown to improve insulin resistance, reduce hyperinsulinaemia, reduce hepatic glucose production and improve both fasting and postprandial glycaemia in NIDDM subjects[25–27].

Recent evidence from animal studies also indicates that this improvement in insulin sensitivity is associated with amelioration of diabetic complications. Thus, troglitazone and pioglitazone reduce blood pressure in insulin-resistant rhesus monkeys[28] and obese Zucker rats[29], and BRL 49653 protects against nephropathy in obese Zucker rats[30,31].

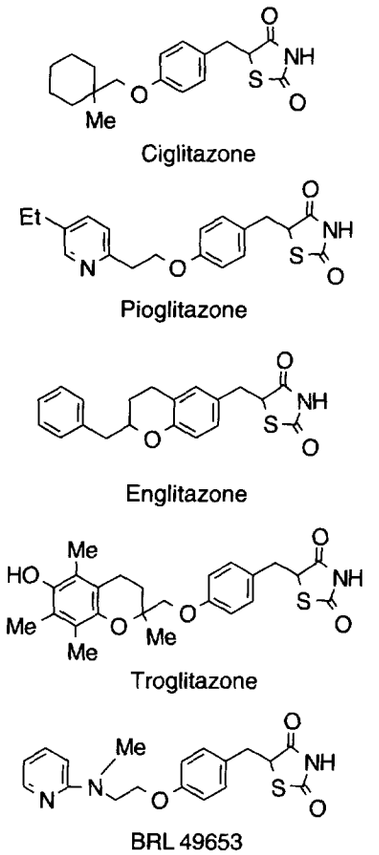

Figure 1. *Chemical structures: the prototype ciglitazone and thiazolidinediones that are, or have been, under clinical investigation.*

Mechanism of action

The mechanism of action of these drugs has not been fully elucidated. Their effects on glucose utilization is insulin-dependent, but the evidence of acute effects on insulin signalling is unconvincing. *In vivo* studies indicate that insulin receptor number (but not affinity) and insulin receptor tyrosine kinase activity are increased after treatment of insulin-resistant animals with thiazolidinediones, but this is most probably a consequence of the fall in plasma insulin levels.

Glucose transport in skeletal muscle and adipose tissue is insulin-sensitive and is normally considered to be rate-limiting for glucose uptake and utilization[32–34]. Both tissues express an insulin-stimulated glucose transporter, GLUT 4, which under basal conditions is located almost exclusively within the cell. After stimulation of glucose uptake by insulin there is, however, an increase in the rate of translocation of GLUT 4 from intracellular storage vesicles and an increase in absolute numbers of GLUT 4 transporters in the plasma membrane[32–34]. In diabetes, however, GLUT 4 function is defective in both skeletal muscle and adipose tissue[34]. In human NIDDM, the protein content of adipose tissue GLUT 4 is reduced and its translocation from intracellular stores in response to insulin stimulation is impaired. Whereas in skeletal muscle GLUT 4 expression is normal, its translocation is impaired and insulin signalling is probably defective[34]. In animal models, GLUT 4 activity, protein and mRNA are, furthermore, reduced in both tissues after β-cell failure[34]. Thus, both impaired GLUT 4 translocation and expression seem central to the development of insulin resistance and impaired glucose uptake in NIDDM.

Treatment of insulin-resistant obese KKA^{Y} mice with pioglitazone corrects the deficiencies in glucose transport and GLUT 4 mRNA and protein abundance in both skeletal muscle and adipose tissue, and this increase in transporter number and function has a strict dependence on the presence of circulating insulin[35]. Similarly, treatment of *ob/ob* mice with BRL 49653 increases the total cellular GLUT 4 content of adipose tissue and increases its translocation to the plasma membrane in an insulin-dependent manner[36]. These effects are, in contrast, less apparent in skeletal muscle, and pioglitazone has been reported to fail to correct defective glucose transport and glucose transporter translocation in skeletal muscle from obese Zucker rats[37]. It has, nevertheless, been shown that thiazolidinediones increase total glucose disposal *in vivo*, and because skeletal muscle is the predominant site of glucose disposal, this suggests that these drugs also affect glucose uptake into muscle. Indeed, Hofman and coworkers[35] have reported that the combination of pioglitazone and insulin restores GLUT 4 mRNA abundance in the soleus muscle of streptozotocin diabetic rats. It appears, therefore, that the effects of thiazolidinediones in increasing insulin-stimulated glucose uptake, at least in adipocytes, can be accounted for by increases in the tissue of total GLUT 4 content, translocation and activity, and it has been suggested that this activity is mainly by stabilization of GLUT 4 mRNA transcripts[38]. Because these effects are dependent on the presence of insulin[35,36], it is probable that thiazolidinediones act to amplify cellular responses to insulin.

Molecular target

Although the molecular mechanisms by which thiazolidinediones exert their effects are not understood, recent evidence may provide some indications. Kletzien and coworkers[39] and Sandouk and coworkers[40] have reported that pioglitazone enhances insulin-regulated 3T3 fibroblast differentiation into mature adipocytes. This effect is totally insulin-dependent and is correlated with an increase in glucose uptake, lipogenesis, and abundance of GLUT 1 and GLUT 4 mRNA. These effects may, therefore, explain the improvement in insulin-stimulated glucose utilization reported *in vivo*. The differentiation of 3T3 cells to adipocytes results from changes in gene expression, among which are those associated with enzymes involved in the metabolism of glucose to fatty acids. Both pioglitazone and insulin have been shown to be required for the maximum expression of enzymes directly involved in conversion of glucose to fatty acids, and it is suggested that this observation is consistent with the premise that thiazolidinediones are active at the level of gene expression[39,40]. The effects on gene expression, at least in 3T3 cells, are not, however, limited to those involved in glucose uptake or utilization – the abundance of fat-specific genes and proteins is also increased[39,40]. This effect on adipocyte differentiation is shared by other thiazolidinediones and it has been suggested that this indicates that they are potent adipogenic agents that, by promoting differentiation, may move cells into a state active for glucose utilization[40]. It has, furthermore, been suggested that the increase in GLUT 4 levels may occur, not because of the direct effects of thiazolidinediones on GLUT 4 gene transcription, but as a consequence of effects on other genes involved with metabolism, or by induction of protein(s) that mediate or enhance the actions of insulin[39].

Kletzien and coworkers[41] have shown that pioglitazone also increased expression of adipocyte fatty acid binding protein (aFABP/AP2) and Harris and Kletzien[42] have reported that there may be a pioglitazone response element in the promoter region of the aFABP gene. The precise cellular function of aFABP is unknown; it is, however, a target for insulin receptor tyrosine kinase activity[43,44] and may, therefore, be involved in insulin signalling in adipocytes and have a role in mediating insulin action in these cells. How thiazolidinediones generate signals to the nucleus to induce gene transcription has also been the subject of intense investigation. Ibrahim and coworkers[45] have demonstrated that the effects of BRL 49653 on expression of the genes that encode proteins involved in fatty acid metabolism are similar to those of natural or unmetabolizable fatty acids and suggested that they activate the same fatty-acid-activated receptor (FAAR). The same authors suggested, furthermore, that this FAAR may be a member of the steroid/thyroid hormone nuclear receptor superfamily. Independently Lehmann and coworkers[46] showed that thiazolidinediones are potent and selective activators of peroxisome proliferator-activated receptor γ (PPARγ), a member of the nuclear receptor superfamily. It is, furthermore, known that PPARγ interacts with a sequence within the aFABP promoter, called ARE-6, which is crucial for expression of the aFABP gene[44], and that there are PPAR response elements in the regulatory regions of several genes that encode enzymes which modulate fatty acid metabolism.

It remains necessary to determine the mechanism whereby activation of PPARγ, responsible for adipogenesis and modulation of lipid metabolism, may account for the overall therapeutic effects of thiazolidinediones and, in particular, their effects on glucose homeostasis in skeletal muscle and liver. Lipotoxicity has, nevertheless, been suggested as an important causative factor in the pathogenesis of obesity-dependent NIDDM (Ref. 47), and insulin resistance induced in animals by high-fat diets is improved by BRL 49653 (Ref. 48). It is, therefore, possible that the marked lipid-lowering effects of these agents, *via* reduced lipolysis and fatty acid oxidation, and increased triglyceride storage, serves to ameliorate the potential effects of elevated free fatty acid levels on insulin resistance.

Whether other ligands for PPARγ also enhance insulin-stimulated glucose uptake and improve insulin sensitivity *in vivo* awaits confirmation. Thiazolidinediones may, however, also activate other members of the steroid nuclear receptor superfamily, independent of those controlling differentiation and maturation, that may play a role in mediating insulin signalling. Because the liver and skeletal muscle are the principal insulin-sensitive tissues it will be interesting to see if thiazolidinediones, by analogy with PPARγ, interact with members of the steroid nuclear receptor superfamily and activate genes involved in glucose utilization in these tissues. Thus, although the delineation of the mechanism of action of thiazolidinediones on preadipocyte differentiation has provided important indications regarding their molecular mechanism of action, it remains to be seen whether this fully explains their *in vivo* biological activity.

Clinical studies

Several thiazolidinediones have been evaluated in clinical trials, but the effects have been reported for darglitazone (Pfizer) and troglitazone (Sankyo/Warner Lambert/Glaxo) only. In a 12-week uncontrolled study in 19 Japanese patients with

NIDDM, troglitazone (400 mg per day oral dose) reduced fasting plasma glucose levels from 11 mM to 8.4 mM and fasting insulin concentrations from 77.4 pM to 56.5 pM. Tolerance to an oral glucose load was also markedly improved, and there was a small but significant fall in the plasma levels of glycated haemoglobin[25]. In a study in 11 obese NIDDM patients, eight[26] showed a marked clinical response to troglitazone (400 mg per day for 6–12 weeks), fasting plasma glucose dropped from 12.7 mM to 8.3 mM. This was accompanied by a fall in hepatic glucose output (28%) and increased glucose disposal. Insulin, free fatty acids and glucagon levels were all significantly reduced by the treatment. In both studies significant lowering of fasting plasma glucose was not observed until after 2–6 weeks of treatment, suggesting that a delay of several weeks may be expected before clinical benefit and antihyperglycaemic efficacy after treatment with these drugs. An improvement in insulin resistance (48% reduction in fasting plasma insulin) and glucose tolerance (40% reduction in the insulin response to oral glucose or mixed meals) has also been reported in obese prediabetic patients (with normal or impaired glucose tolerance)[27], and in nonobese diabetic patients[49] after treatment with troglitazone. Similarly, in a double-blind placebo-controlled study in obese NIDDM patients, darglitazone (25 mg for 14 days) significantly reduced 24-h plasma glucose (20%), insulin (26%), triglyceride (26%) and nonesterified fatty acid profiles (50%) (Ref. 50).

Thus the effectiveness of troglitazone and darglitazone in increasing insulin action in sufferers from NIDDM confirms the potential of thiazolidinediones for the prevention and treatment of this condition. Their effectiveness in improving plasma lipid profiles also indicates that they may be effective in treating Syndrome X. Agents currently reported to be in clinical development are pioglitazone (phase III, Japan), troglitazone (awaiting approval, Japan; phase III, USA) and BRL 49653 (phase II, USA).

β_3-adrenoceptor agonists

The association between obesity, insulin resistance and NIDDM is well recognized[4,51]. Hyperinsulinaemia is associated with glucose intolerance in upper-body obesity and with hypertrophy of abdominal adipocytes[51]. In addition, predominance of upper-body fat is associated with reduced insulin sensitivity[51] and the defect in insulin sensitivity (glucose utilization) in upper body obesity is reported to be quantitatively similar to that seen in overtly hyperglycaemic NIDDM patients. Because epidemiological studies have shown obesity to be a characteristic feature of NIDDM and the insulin resistance Syndrome X (Ref. 9), dietary management has been a mainstay of the control of NIDDM.

Anti-obesity and antidiabetic activity

The potent anti-obesity and antidiabetic properties of agonists at atypical β_3-adrenoceptors in rodents has led to interest in their potential as agents for the treatment of obesity and diabetes[52–58], and several pharmaceutical companies (SmithKline Beecham, Zeneca, Cyanamid, Sanofi, Roche, Ciba Geigy) are, or have been, involved in the discovery of β_3-adrenoceptor selective agonists (Figure 2).

Several studies[56–58] have shown that β_3-agonists (for example BRL 35135, BRL 37344, CL 316243, CGP 12177) elicit a reduction in weight gain or a decrease in body weight of obese, but not lean rodents. This always occurred without a concomitant decrease in food intake, suggesting that it was a consequence of increased thermogenesis. Thus, chronic treatment of obese animals with β_3-agonists causes a sustained increase in metabolic rate, body temperature and 24-h energy expenditure. This reduction in body weight is, furthermore, entirely the result of a reduction in body lipid content, consistent with the potent lipolytic activity of β_3-agonists in rodent white and brown fat and with the dependence of thermogenesis on fat oxidation[56,57].

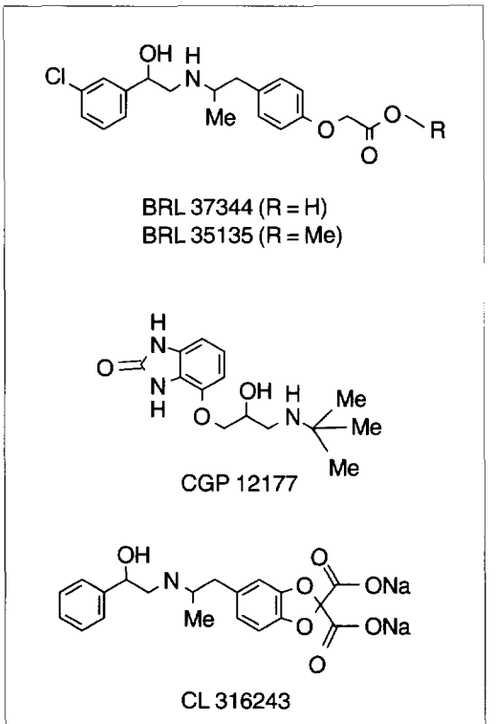

Figure 2. *Chemical structures of some selective β_3-adrenoceptor agonists.*

In addition to their anti-obesity properties, β_3-agonists also exhibit antidiabetic effects in rodent models of NIDDM. In genetically obese (*ob/ob*) mice and Zucker (*fa/fa*) rats, repeat dosing with β_3-agonists improves glycaemic control and insulin sensitivity, as measured by reductions in plasma glucose and insulin levels. In genetically diabetic *db/db*

mice, hyperglycaemia and hyperinsulinaemia are similarly reduced. The antidiabetic effects of both BRL 35135 and CL 316243 are seen at doses that have little or no effect on body weight and are, therefore, unlikely to be secondary to weight loss[56,57].

The mechanism of the antidiabetic effects of β_3-agonists is unclear. As with the thiazolidinediones, the *in vivo* reduction in plasma glucose and insulin levels elicited by BRL 35135, CL 314698 or other β_3-agonists increases with time, suggesting that induction of gene transcription may be involved[56,58]. BRL 35135 has been shown to increase glucose uptake into diaphragm, heart and brown adipose tissue (BAT) of *ob/ob* mice[52] and skeletal muscle in rats[59]. Treatment of *ob/ob* mice with BRL 26830 has, in addition, been found to correct insulin receptor number and kinase activity in adipose tissue and skeletal muscle and to increase glucose transporter numbers[60,61]. Current data suggest, therefore, that β_3-agonists may interact with elements of the insulin signal transduction cascade to improve the sensitivity of target tissues to insulin.

β_3-receptor mutations in diabetes and obesity

Historically the development of β_3-agonists has been largely based on their pharmacology in rodents; the expression of β_3-adrenoceptor mRNA in human adipose tissue, however, raises the possibility that they are also involved in thermogenesis, lipolysis and insulin sensitivity in man. Recent reports support this[62–64], and suggest that a missense mutation in the β_3-adrenoceptor gene could be involved in the development of obesity and NIDDM. Thus Walston and coworkers[62] identified a mutation in the β_3-adrenoceptor gene that results in the replacement of tryptophan by arginine (Trp 64 to Arg) and was associated with the early onset of NIDDM in Pima Indians that were homozygous for the mutation. Similarly, Widen and coworkers[63] identified the same mutation in a group of Finnish patients with NIDDM, in whom it was also associated with early onset of the disease, and Clement and coworkers[64] found the mutation in a group of morbidly obese patients in whom it was associated with an increased capacity to gain weight.

These data therefore provide evidence that the β_3-adrenoceptor is functionally relevant in the control of body weight and insulin sensitivity in man. There are, however, several caveats that should be placed on clinical implications of these findings. In the Finnish[63] study of 128 patients with NIDDM, the mutation was found in only 27; in the study of the Pima Indians[62] only 57 of 642 individuals were homozygous for the mutation. In all three reports, the allelic frequency of the mutation was, furthermore, the same in patients with NIDDM, in those with morbid obesity and in normal subjects. In contrast, in a study of Japanese patients, although the frequency of the mutated allele was similar in NIDDM and non-NIDDM patients, the frequency of the mutation was twofold greater in obese subjects[65]. The clinical importance of the mutation is unclear, but it would seem that it alone is not a major determinant of NIDDM. The mutation in the β_3-adrenoceptor may, nevertheless, be one of several genetic and environmental factors that, in combination, predispose to severe obesity or early onset of NIDDM.

Current data from clinical studies with β_3-agonists are also not encouraging. Although BRL 26830 and BRL 35135 stimulate metabolic rate and improve insulin sensitivity in some subjects, their effect cannot be attributed with certainty to β_3 agonism[56]. Phase I clinical studies with CL 316243 have shown the drug to be well tolerated and to have no side-effects that could be attributable to effects at β_1- or β_2-adrenoceptors. The compound has recently completed phase II trials, but the results of the study have yet to be published. In addition, for those compounds for which results have been published, studies show a lower efficacy in man than in rodents[56].

Screening strategy: human vs rat receptors

Pharmacological comparison has identified differences between β_3-adrenoceptor ligands in cloned receptors from rat and man. Whereas BRL 37344 is a potent full agonist on adenylyl cyclase activity in Chinese hamster ovary (CHO) cell membranes expressing the rat β_3-adrenoceptor, studies show it to be less potent and to have reduced efficacy at the human β_3-receptor. In contrast, CGP 12177 is a partial agonist at both receptors. No such species difference appears to exist for 'classical' β-adrenoceptor ligands (Table 1). Furthermore, although a recent report[66] indicates that BRL 37344 is a full agonist at both human and murine β_3-adrenoceptors, compared with isoprenaline the cyclase stimulation potency of BRL 37344 is 30–40-fold greater at murine β_3-adrenoceptors than at human β_3-adrenoceptors.

Whereas these discrepancies in the pharmacology of the atypical ligands at human β_3-receptors present a confusing picture, they may be explained by differences in receptor density. We have found in CHO cells expressing the human β_3-receptor that as receptor density increases so also does the potency and intrinsic activity of the 'atypical' partial agonists (unpublished data). Thus partial agonist activity, or lack of activity, may reflect low receptor expression. This explanation is, however, unlikely to resolve the discrepancy between the potencies of atypical ligands at human and rat receptors. In a direct comparison of human and rat cloned β_3-receptors at similar expression levels, we have found that the reduced potency and efficacy of BRL 37344 at the human receptor is

Table 1. Comparison of adenylate cyclase activation of Chinese hamster ovary cell membranes expressing the human or rat β_3-adrenoceptor

	Kact[a,b] (μM)	IA[a,c]	Kact[a] (μM)	IA[a]	Kact[d] (μM)	IA[d]	Kact[d] (μM)	IA[d]
	Rat		Human		Rat		Human	
Isoprenaline	5.1	1	4	1	0.66	1	0.65	1
Noradrenaline	7.5	0.8	31	0.9			2.2	0.82
Adrenaline	68	0.75	116	0.8				
BRL 37344	0.44	1	6.6	0.6	0.046	0.88	1.3	0.38
CGP 12177	0.23	0.3	0.26	0.6	0.027	0.26	0.36	0.79

[a]Data from Ref. 67
[b]EC_{50}
[c]IA, intrinsic activity
[d]Unpublished data, Wilson, S. and Chambers, J. (SmithKline Beecham, Welwyn, Herts, UK)

Table 2. Comparison of pD_2 values and intrinsic activity of β-adrenoceptor agonists on lipolysis in adipocytes[a]

	Human		Human				Rat			
	Ref. 68		Ref. 69		Ref. 70		Ref. 70		Ref. 68	
	pD_2[b]	IA[c]	pD_2	IA	pD_2	IA	pD_2	IA	pD_2	IA
Isoprenaline	8.0	1	10.5	1	7.6	1	7.6	1	8.09	1
Noradrenaline	6.6	1			6.25	0.93	6.9	1	7.17	1
Adrenaline					6.3	0.98	6.8	0.94		
BRL 37344	ND[d]	<0.1	6.23	0.6	5.5	0.18	8.6	1	8.72	1
CGP 12177	ND	<0.1	7.31	0.4					6.6	0.68

[a]Data from Refs 68–70
[b]–log EC_{50}
[c]IA, intrinsic activity
[d]ND, not detectable

maintained (Wilson, S. and Chambers, J., unpublished observations). Assessment of the agonist activity of BRL 37344 and CGP 12177 in rat and human adipose tissue indicate, furthermore, that they are substantially less potent and are partial agonists as stimulants to lipolysis in man (Table 2).

Thus although BRL 37344 is a potent and full agonist on CHO cells expressing the rat β_3-adrenoceptor and in rat adipocytes, the consensus in the literature shows it to be less potent and a partial agonist in human white adipose tissue (WAT) adipocytes and on human cloned β_3-adrenoceptors.

Are β_3-agonists lipolytic in man?

Although the involvement of the atypical β_3-adrenoceptor in thermogenesis and lipolysis in rodents is well established, their presence and function in human adipose tissue is less clear. Radioligand binding studies indicate the presence of β_1-, β_2- and β_3-adrenoceptors on rat adipocytes; the atypical β_3 sites are, however, abundant and represent approximately 80% of the total radioligand binding sites[71]. In human adipose tissue there is conflicting evidence for β_3-adrenoceptor expression. Although the human gene coding the β_3-adrenoceptor has been identified, studies by Thomas and Liggett[72] suggest that it is only poorly expressed in human adipose and other metabolic tissues. Kreif and coworkers[73] have, in contrast, reported that β_3-adrenoceptor mRNA is highly expressed in deep adipose tissue deposits, such as perirenal and omental, where it is associated with uncoupling protein. The issue of β_3-adrenoceptor expression and distribution in adults remains to be clarified, as does the more fundamental question of whether β_3-adrenoceptors are functionally relevant in man.

Lonnqvist and coworkers[70] have shown BRL 37344 and CGP 12177 to be lipolytic in human adipocytes, but they are considerably less potent (3 log units) than isoprenaline and are partial agonists (Table 2). The lipolytic response to BRL 37344 was, in addition, inhibited by β_1- and β_2-receptor antagonists, indicating an unselective mechanism of action. In the same

studies, the lipolytic activity of CGP 12177 was unaffected by β_1- and β_2-adrenoceptor blockade, suggesting that the 'atypical' receptor is expressed in human white fat cells; its intrinsic activity was, however, only 30% that of isoprenaline. These data suggest, therefore, that the lipolytic response to sympathomimetics in human WAT is principally coupled to β_1- and β_2-adrenoceptors. Similarly, Bousquet-Melou and coworkers[68] have reported that BRL 37344, CL 316243 and CGP 12177 are ineffective in human fat cells and that the lipolytic activity of catecholamines in human white fat is mediated by β_1- and β_2-adrenoceptors. It is, therefore, suggested that the β_3-adrenoceptor is functionally redundant or poorly coupled to adenylate cyclase in human white fat. It can, nevertheless, be argued that the functionally relevant metabolic tissue in man is BAT, which, because of its poorly defined distribution and relative sparsity is more difficult to study. The thermogenic and antidiabetogenic activity of β_3-agonists may, alternatively, be unrelated to effects on adipose tissue metabolism and more associated with skeletal muscle energy expenditure and insulin sensitivity.

Finally, whereas polymorphisms in the β_3-adrenoceptor gene suggest that this may be a susceptibility (mutation) gene for development of NIDDM, it will be interesting to determine the effect of this mutation on β_3-adrenoceptor ligand binding or signal transduction, and thence the therapeutic utility of selective β_3-agonists. It is, however, probable that the question of the functional and clinical importance of the β_3-adrenoceptor in NIDDM will be resolved only when highly selective and potent β_3-agonists, optimized for the human receptor by SAR studies, are studied clinically for their anti-obesity and antidiabetogenic activity.

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What place for R&D in tomorrow's drug industry?

Gary Johnson

The relative merits of just three strategies will determine the future of R&D. The pharmaceutical industry has embarked on a bewildering frenzy of restructuring; companies announce new acquisitions and alliances seemingly on a daily basis. However, taking a step back, there are only three 'mega-strategies' open to them. First, horizontal integration – acquisition of other pharmaceutical products through, for example, a merger; second, vertical integration – acquisition of customers, who may be distributors or even healthcare providers; finally, R&D. These are the strategies that are competing for investment funds. This article explores the real long-term promise in each of these strategies and the implications for drug discoverers and developers.

Healthcare systems vary enormously across the globe, but they have shared one thing in common for many decades: an inability to curb relentless growth in healthcare spending. During the last decade, however, new circumstances have allowed, or forced, something to be done.

We seem to have a problem

In the USA, a huge glut of physicians caused a power-shift from physicians to payers; managed-care got a foothold. Meanwhile, government deficits in Germany and Italy forced drastic action on government spending. In the UK, right-wing, market-oriented politics gave another incentive for radical change.

There is nothing really new in the measures that the market (in the USA) or governments (in Europe) have imposed. In the States, managed-care has been around, albeit as a marginal player, for decades. In Europe, a vast array of government measures to curb prices and costs has been a part of the landscape for as long as some can remember. It is the range and severity of price and cost controls operating in any given country that has increased.

It couldn't have come at a worse time

Just as burgeoning health cost controls are forcing down the rewards of pharmaceutical R&D (i.e. sales), so ever-tougher regulatory hurdles are forcing up R&D costs. As an indicator, the average number of pages per NDA grew from less than 40,000 to more than 90,000 in the course of the last decade. The cost of developing a new product (including the costs of capital and failure) has grown from an estimated $87 million in 1982 to more than $350 million in 1983[1].

It is not surprising, then, that the number of new product introductions per year has not increased. Indeed, just holding the number of introductions constant, which is what the industry has achieved, has resulted in R&D spending growing from 12% to 19% of sales between 1980 and 1994 in the USA[1]. Not only are R&D costs exploding, but other allied costs are growing fast as well. In particular, manufacturing (where overall costs are now higher than they are for R&D) is a strategic issue; major investments are required pre-approval.

Are we sure we have a problem?

In spite of this tougher environment, the pharmaceutical industry is one of the most profitable on earth, with returns on capital employed, pre-tax profit margins and returns on shareholders' funds around threefold those seen in other

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