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β_3-Adrenoceptor agonists: potential, pitfalls and progress

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Abstract

β_3-Adrenoceptor agonists are very effective thermogenic anti-obesity and insulin-sensitising agents in rodents. Their main sites of action are white and brown adipose tissue, and muscle. β_3-Adrenoceptor mRNA levels are lower in human than in rodent adipose tissue, and adult humans have little brown adipose tissue. Nevertheless, β_3-adrenoceptors are expressed in human white as well as brown adipose tissue and in skeletal muscle, and they play a role in the regulation of energy balance and glucose homeostasis. It is difficult to identify β_3-adrenoceptor agonist drugs because the pharmacology of both β_3- and β_1-adrenoceptors can vary; near absolute selectivity is needed to avoid $\beta_{1/2}$-adrenoceptor-mediated side effects and selective agonists tend to have poor oral bioavailability. All weight loss is lipid and lean may actually increase, so reducing weight loss relative to energy loss. β_3-adrenoceptor agonists have a more rapid insulin-sensitising than anti-obesity effect, possibly because stimulation of lipid oxidation rapidly lowers intracellular long-chain fatty acyl CoA and diacylglycerol levels. This may deactivate those protein kinase C isoenzymes that inhibit insulin signalling.

Keywords: β_3-Adrenoceptor; β_4-Adrenoceptor; β_3-Adrenoceptor agonist; Thermogenesis; Obesity; Diabetes

1. Introduction

Although the β_3-adrenoceptor was not cloned until 1989 (Emorine et al., 1989), it had already been apparent for 5 or 6 years that agonists of this receptor might have potential in the treatment of obesity and Type 2 diabetes (Arch and Ainsworth, 1983; Arch et al., 1984a). Early evidence for the β_3-adrenoceptor stemmed from the discovery that β_1- and β_2-adrenoceptor antagonists lacked potency in various gut preparations and as antagonists of β-adrenoceptor agonist-driven lipolysis. Then in the early 1980s, novel β-adrenoceptor agonists were discovered to be more potent as stimulants of rat white or brown adipocyte lipolysis than as stimulants of atrial contraction, or tracheal or uterine relaxation (Arch et al., 1984a). These compounds were found to stimulate metabolic rate and to have anti-obesity and anti-diabetic (insulin-sensitising) activity in rats and mice (Arch et al., 1984b; Meier et al., 1984; Yen et al., 1984; Cawthorne et al., 1984).

Since that time, numerous studies have produced similar results in rodents for other β_3-adrenoceptor agonists (e.g. Umekawa et al., 1997; Kiso et al., 1999); the β_3-adrenoceptor and β_3-adrenoceptor agonists have been reviewed regularly (Arch and Kaumann, 1993; Arch, 2001; Dow, 1997; Weyer and de Souza, 2000), and there have been two books on the subject (Goldberg and Frishman, 1995; Strosberg, 2000). No β_3-adrenoceptor agonist has, however, advanced beyond Phase II clinical studies. In this brief review, I shall describe the status and discuss the potential of β_3-adrenoceptor agonists for the treatment of obesity, touching also upon Type 2 diabetes. First though, I shall describe some of the problems of identifying β_3-adrenoceptor agonists suitable for development as drugs.

2. Identification of β_3-adrenoceptor agonists for development

2.1. Rodent vs. human receptors

The first generation β_3-adrenoceptor agonists were identified largely from studies in vivo in rats and mice. These compounds were therefore optimised for selectivity at the rodent β_3-adrenoceptor. When the human β_3-adrenoceptor was cloned and expressed by Strosberg et al. (Emorine et al., 1989), one of the first generation compounds [(*RR*+*SS*)-(±)-4-[2-(2-(3-chlorophenyl)-2-hydroxyethyl)amino)pro-

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pyl]phenoxyacetate (BRL-37344)] was shown to be a potent stimulant of cyclic AMP synthesis. It was subsequently realised, however, that the first generation agonists have poor efficacy at the human β_3-adrenoceptor (Wilson et al., 1996; comment in introduction of Fisher et al., 1998): their efficacy may be sufficient to stimulate adenylyl cyclase in cells transfected with high numbers of the β_3-adrenoceptor, but in human white adipocytes, they elicit either little or no response, or a response mediated via the β_1- or β_2-adrenoceptor (Hoffstedt et al., 1996).

To resolve this problem, a number of pharmaceutical companies have used human cloned β-adrenoceptors to identify agonists with increased efficacy and potency at the β_3-adrenoceptor, and reduced efficacy and potency at the β_1- and β_2-adrenoceptors. Our own experience suggests that any efficacy at β_1- or β_2-adrenoceptors is a liability. For example, the β_3-adrenoceptor agonist (*RR*)-5-{2-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]propyl}-1,3-benzodioxole-2,2-dicarboxylate (SB-220646) had little or no agonist activity at cloned β_1- and β_2-adrenoceptors, and yet, its stimulation of human white adipocyte lipolysis was antagonised by nadolol at a concentration that blocks β_1- and β_2-, but not β_3-adrenoceptors. Moreover, SB-220646 was a full agonist of the force of contraction of human right atrial appendage, and studies with selective antagonists showed that both the β_1- and β_2-adrenoceptors were involved (Sennitt et al., 1998). The explanation for such findings is presumably that human tissues possess many β_1- or β_2-adrenoceptors and very few β_3-adrenoceptors (Strosberg and Gerhardt, 2000; Chamberlain et al., 1999). It is, nevertheless, possible to stimulate lipolysis exclusively via the β_3-adrenoceptor in human white adipocytes using a suitably selective agonist, such as (*S*)-4-{2-[2-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl}phenoxymethylcyclohexylphosphinic acid lithium salt (SB-226552) (Sennitt et al., 1998) or 4-{1-[2-(*S*)-hydroxy-3-(4-hydroxyphenoxy)-propylamino]cyclopentylmethyl}phenoxymethyl)phenyl-phosphonic acid lithium salt (SB-251023) (Arch et al., 1999).

Thus, the challenge of identifying highly selective and effective β_3-adrenoceptor agonists to selectively stimulate the low numbers of β_3-adrenoceptors in human tissues is compounded by differences in pharmacology between the rodent and human β_3-adrenoceptors, making in vivo studies in rodents potentially misleading. Not only do agonists display significant differences in efficacy and potency between rodent and human β_3-adrenoceptors, but antagonist potencies may also vary. The β_3-adrenoceptor is often described as being blocked by the selective β_3-adrenoceptor antagonist (3-(2-ethyl-phenoxy)-1-[(1*S*)-1,2,3,4-tetrahydronaphth-1-ylamino]-(2*S*)-2-propanol oxalate (SR-59230A). However, while this compound may be a selective antagonist of the rodent β_3-adrenoceptor (Manara et al., 1996; Kubo et al., 1997 but see Kaumann and Molenaar, 1996), its utility as a selective antagonist of the human β_3-adrenoceptor is less certain (Arch, 2000). Recently, two selective antagonists of the human cloned β_3-adrenoceptor, (*S*)-*N*-[4-[2-[[3-[3-(aminosulphonyl)phenoxy]-2-hydroxypropyl]-amino]ethyl]phenyl]benzenesulfonamide (L-748328) and (*S*)-*N*-[4-[2-[[3-[3-(acetamidomethyl)phenoxyl]-2-hydroxypropyl]amino]-ethyl]phenyl]benzenesulfonamide (L-748337), have been described, but these compounds do not bind to the rodent β_3-adrenoceptor (Candelore et al., 1999).

2.2. The "β_4"-adrenoceptor

β_3-Adrenoceptor agonists fall into two main chemical classes: arylethanolamines and aryloxypropanolamines (a third class is the trimetoquinols). The aryloxypropanolamine structure is typical of β-adrenoceptor antagonists, and some β_3-adrenoceptor agonists [e.g. (*S*)-6-(4-(2-((3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl) amino)-2-methylpropyl)phenoxy)-3-pyridinecarboxamide monohydrochloride (LY-377604)], but not others (e.g. SB-226552; SB-251023), retain significant $\beta_{1/2}$-adrenoceptor antagonist potency (Miller et al., 1999; Sennitt et al., 1998). There are other, highly potent $\beta_{1/2}$-adrenoceptor antagonists [e.g. cyanopindolol; (±)-4-(3-*t*-butylamino-2-hydroxypropoxy)benzimidazol-2-one (CGP-12177)] which are β_3-adrenoceptor agonists at higher concentrations than those which block the β_1- or β_2-adrenoceptor. The problem with these latter compounds, notably CGP-12177, is that in tissue studies, they also display a pharmacology that has been ascribed to a "β_4"-adrenoceptor. This pharmacology (Table 1) has been elucidated mainly by Kaumann, Molenaar and colleagues (Kaumann, 1997) using animal and human cardiac tissue, but a similar pharmacology has been reported for CGP-12177 in human white adipocytes (Galitzky et al., 1997). Like β_3-adrenoceptors, "β_4"-adrenoceptors are insensitive to standard $\beta_{1/2}$-adrenoceptor antagonists.

The "β_4"-adrenoceptor has never been cloned despite serious attempts to do so (Strosberg and Arch, 2000), and now that the full human genome is known, it is clear that it is not a distinct molecular entity, but rather a form of the β_1-

Table 1
Comparison of β_1-, β_3-and β_4-adrenoceptor pharmacology in tissues and human cloned β-adrenoceptors

	Tissues		Cloned receptors		
	β_3	β_4	β_3	β_4	β_1
Agonist pEC_{50}					
CGP-12177	5.2[a]; 6–8	7–7.5	7.1	7.9	antag
Antagonist pK_B					
(−)-Propranolol	6–7	<5.7	7.0	7.1	8.0
CGP-20712A	4.8–5.6	6.3–6.4	4.8	7.4	8.4

Antagonists pK_B values were obtained using CGP-12177 as the agonist for β_4-adrenoceptor pharmacology, and isoprenaline or β_3-adrenoceptor agonists for β_1- and β_3-adrenoceptor pharmacology. Sources are Konkar et al. (2000b) for cloned β_1- and "β_4"-adrenoceptor, Kaumann (1997) and Arch and Kaumann (1993) for tissues and Arch (2000) for the cloned β_3-adrenoceptor.

[a] Human ventricle.

adrenoceptor. Konkar et al. have shown that the human cloned β_1-adrenoceptor is activated by CGP-12177 and this activation is less sensitive than is activation by isoprenaline to blockade by selective and nonselective $\beta_{1/2}$-adrenoceptor antagonists (Table 1). This evidence is not conclusive because pK_B values for cloned β_1-adrenoceptors showing "β_4"-adrenoceptor pharmacology are higher than those for tissue "β_4"-adrenoceptor pharmacology. Studies using tissues from knockout mice are compelling, however. CGP-12177 stimulated adenylyl cyclase in brown adipose tissue membranes from wild-type mice via high and low affinity sites. The low affinity site was absent in mice lacking the β_3-adrenoceptor, whereas the high affinity site was absent in mice lacking the β_1-adrenoceptor. Although it was clearly a β_1-adrenoceptor, the high affinity site displayed resistance to propranolol and greater sensitivity than the β_3-adrenoceptor to the β_1-adrenoceptor antagonist (±)-[2-(3-aminocarbamoyl-4-hydroxyphenoxy)ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)phenoxy]-2-propanol hydrochloride (CGP-20712A) (Konkar et al., 2000a), which is typical of "β_4"-adrenoceptor pharmacology (Table 1). Subsequent work showed that another aryloxypropanolamine, 6-(4-{2-[(*S*)-2-hydroxy-3-(2-oxo-2,3-dihdro-1*H*-benzoimidazol-4-yloxy)-propylamino]-2-methyl-propyl}-phenoxy)-nicotinamide (LY-362884), displayed similar properties to CGP-12177 in human and rat cloned β_1-adrenoceptors. By contrast, SB-251023 does not appear to activate the "β_4"-adrenoceptor conformation of the β_1-adrenoceptor (Konkar et al., 2000b), consistent with it failing to stimulate human right atrial appendage contractility via the "β_4"-adrenoceptor (Sennitt et al., 1998). SB-251023 is also an aryloxypropanolamine, so this structural type is not necessarily associated with "β_4"-adrenoceptor agonism. Recently, Kaumann et al. (2001) have also concluded that the "β_4"-adrenoceptor is an atypical state of the β_1-adrenoceptor. They found that (−)-CGP-12177 was a cardiac stimulant in atria from β_2-adrenoceptor knockout but not $\beta_{1/2}$-adrenoceptor double knockout mice (Kaumann et al., 2001).

Kompa and Summers (1999) had predicted that the β_4-adrenoceptor was a form of the β_1-adrenoceptor because responses displaying the two pharmacologies desensitised and resensitised in parallel in a rat model of cardiac failure (Kompa and Summers, 1999). There is a recent report, however, that β_1- but not β_4-adrenoceptor-mediated responses desensitise in response to foot shock stress (Santos and Spadari-Bratfisch, 2001). It therefore appears that these two pharmacological manifestations of the same molecular entity can be differentially regulated.

Since most of the evidence for functional β_3-adrenoceptors in human tissues is derived from studies using CGP-12177, these findings raise the question of whether there really are functional β_3-adrenoceptors in man. But while studies using CGP-12177 must be interpreted with caution, there is other evidence that the β_3-adrenoceptor mediates lipolysis in human white adipocytes. Disodium (*RR*)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1,3-benzodioxazole-2,2-dicarboxylate (CL-316243), SB-262552 and SB-251023, which have no β_1-adrenoceptor agonist activity and, in contrast to "β_4"-adrenoceptor agonists, do not stimulate atrial tissue, each stimulate human white adipocyte lipolysis via non-$\beta_{1/2}$-adrenoceptors (Hoffstedt et al., 1996; Sennitt et al., 1998; Arch et al., 1999). Non-"β_4"-adrenoceptor agonists have also been used to demonstrate the presence of functional β_3-adrenoceptors in other human tissues (Igawa et al., 1999; Gauthier et al., 2000).

2.3. Whole cell, membrane and binding assays

Most pharmaceutical companies have evaluated their β_3-adrenoceptor agonists by measuring cyclic AMP accumulation in whole cells transfected with the human β_3-adrenoceptor. Workers at SmithKline Beecham, by contrast, used membranes isolated from such cells to measure cyclic AMP production by adenylyl cyclase (Sennitt et al., 1998). Not only are the agonists usually more potent in the whole cell assay, but relative potencies differ between the two assays, the arylethanolamine being more potent relative to the aryloxypropanolamine in the whole cells compared to the membrane assay. Moreover, in binding assays employing [^{125}I]-iodocyanopindolol as the labelled ligand, the relative potencies of a series of agonists were almost the complete opposite of their relative potencies as stimulants of cyclic AMP accumulation (Table 2).

Kenakin (1997) has highlighted a problem in comparing functional and binding affinities. This is that the labelled antagonist binds to the receptor whatever G protein the receptor is linked to; consequently, binding reflects the interaction of the unlabelled agonist with all the states of the receptor. Functional studies, on the other hand, may reflect the interaction of the agonist with the receptor when it is bound to only one G protein—in the present case, that which links it to adenylyl cyclase. This cannot explain the different results in the two functional assays (whole cell cyclic AMP accumulation and membrane adenylyl cyclase),

Table 2
Relative affinities of agonists at human cloned β_3-adrenoceptors vary with assay

	Function: K_a		Binding: K_i
	cAMP cells	Cyclase membranes	vs. [^{125}I]ICYP membranes
(−)-Isoprenaline (μM)	0.014	3.9	30
Relative $K_{a/i}$ values			
(−)-Isoprenaline	(1)	(1)	(1)
(−)-Noradrenaline	7.9	2.4	5.0
BRL-37344	14	0.43	0.22
CGP-12177	101	1.2	0.017
Cyanopindolol	229	1.5	0.0027

Data are taken from Wilson et al. (1996).

however. To attempt to explain the latter finding, one might argue that relative potencies of agonists can vary between functional assays if the agonists vary in efficacy: high affinity/low efficacy compounds (e.g. BRL-37344?) rank better in assays where receptor number or coupling is high (whole cells?), whereas high efficacy/low affinity compounds (e.g. cyanopindolol: CGP-12177) rank better in assays where receptor number or coupling is low (membranes) (Kenakin, 1984). This does not appear to explain the data shown in Table 2, however, since although BRL-37344 had a lower intrinsic activity (and presumably lower efficacy) than cyanopindolol or CGP-12177 in the membrane assay, this was not so in the whole cell assay (Wilson et al., 1996).

An alternative explanation for these findings is that β_3-adrenoceptor agonists can bind to the β_3-adrenoceptor in (at least) two ways. One conformation is favoured by the arylethanolamines and predominates in whole cells; the other conformation, favoured by aryloxypropanolamines, is more common in membranes. In the membrane binding assay, the labelled aryloxypropanolamine iodocyanopindolol will bind almost exclusively to the conformation of the β_3-adrenoceptor that is more common in membranes and preferred by aryloxypropanolamines. The ability of an unlabelled ligand to displace the labelled iodocyanopindolol will then depend only on its affinity for this one form of the receptor, though it might have a very different affinity for the other form. The "β_4"-adrenoceptor story may have a similar explanation: β-adrenoceptor ligands may bind to the β_1-adrenoceptor in two ways, the site with lower affinity for aryloxypropanolamines such as CGP-12177 producing a cellular signal (Fig. 1).

Although in this explanation, I have used the concept of binding affinity as though it is distinct from efficacy, it is important to recognise that binding depends not only on the affinity of the initial binding step, but also on the extent to which the conformation of the receptor changes once the ligand becomes bound (Colquhoun, 2001). Therefore, the argument could be rephrased in terms of compounds having differing efficacies for the two forms of each receptor. As discussed above, it does appear that BRL-37344 has a lower efficacy than CGP-12177 in the membrane but not the whole cell assay.

These findings raise the question of which assay is most predictive of β_3-adrenoceptor agonist activity in human tissues. One might expect that a whole cell assay would be more predictive than a membrane assay, but potencies in the membrane assay are in general the more predictive of potencies in human white adipocyte lipolysis experiments (Sennitt, unpublished). Moreover, the blood levels and doses of β_3-adrenoceptor agonists reported to stimulate metabolic rate in man seem high in relation to the EC_{50} values for the same compounds in whole cell assays (Arch, 2000; Miller et al., 1999; Van Baak et al., 2000; Mathvink et al., 2000). While it may seem from the discussion above that the nature of the assay is only an issue when comparing

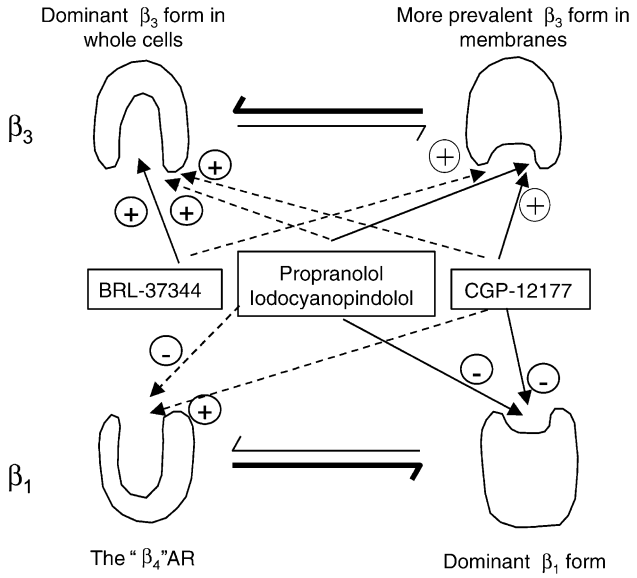

Fig. 1. β_3- and β_1-adrenoceptors display at least two pharmacologies: a speculative explanation. Two extreme conformations of the β_3-adrenoceptor and the β_1-adrenoceptor are illustrated, together with the relative affinities (dashed lines indicate lower affinity) of ligands for these conformations as agonists (+) or antagonists (−). BRL-37344 is an example of an arylethanolamine agonist, and CGP-12177 is shown as an example of an aryloxypropanolamine agonist of the β_3- and "β_4"-adrenoceptors. Propranolol and iodocyanopindolol are aryloxypropanolamines that are usually viewed as antagonists, but propranolol at least has some agonist activity at the β_3-adrenoceptor expressed in intact cells (see Arch, 2000). Since the β_1- and β_3-adrenoceptors have different primary structures, the balance of the two conformations differs between them. The difference in primary structures also results in BRL-37344 having little affinity for either form of the β_1-adrenoceptor. This hypothesis builds on ideas in the discussion of Konkar et al. (2000b). β_3- and β_1-adrenoceptors display at least two pharmacologies: a speculative explanation.

arylethanolamines and aryloxypropanolamines, our recent experience is that the relative potencies of even a group of structurally similar compounds can vary markedly according to the assay used (Miller and Chambers, unpublished).

2.4. Oral bioavailability

The identification of a selective agonist or antagonist of a receptor is a long way from the synthesis of a compound that might become a drug. Issues of metabolism, clearance, drug interactions and toxicity have to be addressed. In the case of β_3-adrenoceptor agonists—at least those designed for the human receptor—oral bioavailability has proved to be a particular problem. Workers from Pfizer and Bristol Myers Squibb have reported on the poor oral bioavailability of their compounds (see Arch, 2000) and Merck produced a number of papers describing compounds with poor oral bioavailability before identifying a selective β_3-adrenoceptor agonist suitable for oral administration to man (Mathvink et al., 2000). LY-377604 from Eli Lilly, which has been administered to man (Miller et al., 1999), has been described as having 20% oral bioavailability in preclinical studies (Shuker et al., 1999).

3. Expectations of a β_3-adrenoceptor agonist

3.1. Role of the β_3-adrenoceptor in man

The key sites of action for β_3-adrenoceptor agonists appear to be skeletal muscle (Astrup et al., 1985), brown adipose tissue (Foster and Frydman, 1978) and (not as a site of thermogenesis but as a source of fuel) white adipose tissue (Schiffelers et al., 1998; Havel et al., 1964). For a fuller discussion, see Arch (2001). β_3-adrenoceptor mRNA is expressed in lower amounts in human than in rodent adipose tissue and the promoter for the human β_3-adrenoceptor appears to drive expression of the mRNA predominantly in brown adipose tissue (Ito et al., 1998). Since there is relatively little brown adipose tissue in adult humans, one would not expect as marked effects of β_3-adrenoceptor agonists in humans as in rodents. There are, nevertheless, a number of arguments that suggest that β_3-adrenoceptor agonists might be of value in the treatment of human obesity and Type 2 diabetes.

Firstly, much of the thermogenic response to β_3-adrenoceptor agonists does not take place in brown adipose tissue, even in rodents. The thermogenic effect of the β_3-adrenoceptor agonist CL-316243 in mice that lacked brown adipose tissue was still 50% of that in wild-type mice (Lowell et al., 1993), and in warm-acclimated rats, most of the thermogenic response to (*RR*+*SS*)-(±)-4-[2-(2-hydroxy-2-phenyl-ethylamino)-propyl]-benzoic acid (BRL-28410) seemed to occur in skeletal muscle rather than brown adipose tissue (Thurlby and Ellis, 1986). Secondly, although β_3-adrenoceptor mRNA is detected primarily in adipose tissue, immunohistochemical studies have demonstrated the presence of β_3-adrenoceptor protein in a number of other human tissues, including skeletal muscle (Chamberlain et al., 1999).

Thirdly, the Trp64Arg polymorphism of the β_3-adrenoceptor gene has been linked with a predisposition to obesity and diabetes in a number of studies. The link is subtle and a similar number of studies have failed to detect any link (Allison et al., 1998; Fujisawa et al., 1998), but given that the polymorphism has only a small effect on function (Umekawa et al., 1999; Hoffstedt et al., 1999; Pietri-Rouxel and Strosberg, 1995) and that there are probably a number of genes that contribute to the genetic component of obesity, it is remarkable that any link has been detected.

Fourthly, there is some evidence that the thermogenic effects in humans of non-β_3-adrenoceptor-selective sympathomimetic agents (isoprenaline and ephedrine) is partially (40%) insensitive to a dose of nadolol that blocks β_1- and β_2-adrenoceptors (Wheeldon et al., 1993; Liu et al., 1995), though conflicting evidence has also been described (Schiffelers et al., 2000).

For further evidence of the potential of β_3-adrenoceptor agonists in humans, one must turn to the effects that these compounds have actually elicited in humans and other primates.

3.2. Effects of β_3-adrenoceptor agonists in humans and monkeys

Some of the first generation β_3-adrenoceptor agonists stimulated metabolic rate in humans, but they also had β_1- or β_2-adrenoceptor-mediated side effects, raising the possibility that their thermogenic activity was mediated via these receptors (see Clapham et al., 2001). More recently, LY-377604 (120 mg), which is a β_1- and β_2-adrenoceptor antagonist, was reported to stimulate oxygen consumption by 17.5% in normal weight to moderately obese men (Miller et al., 1999). *N*-{4-[2-((*R*)-2-hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenyl}-4-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonamide (L-796568) (1000 mg) from Merck had a much smaller effect in obese men (no more than 5%) and at a lower dose (250 mg), it was ineffective (Van Baak et al., 2000). Another Merck compound, 4-(3-hexyl-ureido)-*N*-(4-{2-[(*S*)-2-hydroxy-3-(4-hydroxy-phenoxy)-propylamino]-ethyl}-phenyl)-benzenesulfonamide (L-755507), has been demonstrated to raise metabolic rate and serum glycerol levels when infused i.v. in rhesus monkeys at lower dose levels than those which raise heart rate. Isoprenaline, by contrast, was more potent as a stimulant of heart rate than of lipolysis (Fisher et al., 1998). These results clearly indicate the presence of functional β_3-adrenoceptors in this species.

Only the first generation compound (*RR*+*SS*)-(±)-methyl 4-[2-[(2-hydroxy-2-phenylethyl)amino]propyl]-benzoate, (*E*)-2-butenedioate (2:1) salt (BRL-26830A) has been reported to enhance weight loss in man (Zed et al., 1985; Connacher et al., 1988). Not all anti-obesity studies on this compound showed weight loss (Chapman et al., 1987), however, and since BRL-26830A also elicited the β_2-adrenoceptor-mediated side effect of tremor, one cannot be certain that weight loss, when it occurred, was due to β_3-adrenoceptor stimulation. In rodents, all the weight loss elicited by β_3-adrenoceptor agonists is fat and when the

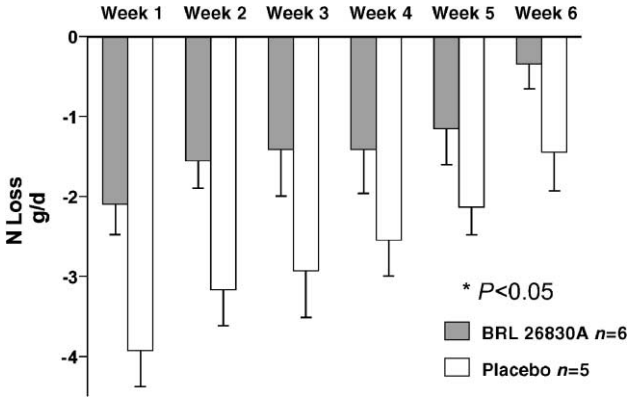

Fig. 2. BRL-26830 restricts protein loss in obese men. Subjects were strictly observed in a hospital ward and fed on a liquid diet that gave 8375 kJ less than required for weight maintenance with a 42% decrease in protein intake during weight maintenance. The dose of BRL-26830A was 100 mg qds (Abraham et al., 1987). BRL-26830 restricted protein loss in obese men.

Table 3
Drugs that produce the same energy loss may have very different effects on body weight

		"Pure" anorectic agent (15% lean tissue)	Lipid loss only	Protein preservation[a]
Lean tissue (1 kcal/g)	g/week	−37	0	+175
	kcal/week	−37	0	+175
Adipose[b] (7 kcal/g)	g/week	−212	−217	−242
	kcal/week	−1484	−1521	−1696
Body weight	g/week	−250[c]	−217	−67
	kcal/week	−1521	−1521	−1521

[a] Preservation of protein from Abraham et al. (1987).
[b] Since weight loss is exclusively lipid and not even the non-lipid component of adipose tissue appears to be lost, it may be more appropriate to replace adipose (7 kcal/g) by lipid (9 kcal/g), which would produce even greater differences in weight loss for the three columns.
[c] Average weekly weight loss due to anorectic drugs (Kolanowski, 1999).

compound is given with food, there may actually be an increase in lean tissue (Arch et al., 1989). In man, BRL-26830A similarly reduced the loss of nitrogen in obese subjects on a liquid, low calorie diet (Abraham et al., 1987) (Fig. 2). Again, this might be a β_2-adrenoceptor-mediated effect.

This selective action on lipid has implications for the rate of weight loss that one might expect to achieve with a β_3-adrenoceptor agonist. Restriction of energy intake results in weight loss that is about 15% lean tissue (Durrant et al., 1980), and lean tissue (being 75% water) has an energy content of only about 1 kcal/g, whereas adipose tissue, with its low water content, contains 7 kcal/g. Therefore, for the same effect on energy balance, a drug that selectively stimulates lipid oxidation will have only 87% of the effect on body weight as one that solely reduces food intake. Moreover, if protein is retained to the extent found in the study on BRL-26830 (Fig. 2), this percentage falls to 27% (Table 3). Presumably, protein retention cannot continue indefinitely and the benefit of β_3-adrenoceptor agonists may be seen in the longer term.

A number of groups have reported that β_3-adrenoceptor agonists improve insulin sensitivity in rodents at dose levels or over time periods that do not affect body weight (Cawthorne et al., 1992; Bryson et al., 1999; Largis et al., 1994; Kiso et al., 1999; Williams et al., 1999). In rhesus monkeys, (4-{(*R*)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propylamino}-2,3-difluoro-phenyl)-acetic acid (GR-265261-X) reduced insulin (and triglyceride) levels without affecting body weight (Hansen, 2000). Similarly in humans, 10-day treatment with *RR*+*SS*-(±)-methyl-4-[2-[2-hydroxy-2-(3-chlorophenyl)ethylamino]-propyl]-phenoxyacetate hydrobromide (BRL-35135) improved insulin sensitivity in obese diabetic subjects without affecting body weight (Smith et al., 1990). BRL-35135 causes tremor, so its effect may have been mediated by the β_2-adrenoceptor. Studies on CL-316243 are easier to interpret since it has no β_1- or β_2-adrenoceptor-mediated side effects in man. CL-316243 enhanced insulin action (at 4 weeks) and reduced respiratory quotient (at 8 weeks) in healthy lean men without affecting body weight (Weyer et al., 1998). L-796568 given for 28 days reduced plasma triglycerides in man without affecting body weight or eliciting β_1- or β_2-adrenoceptor-mediated side effects, but changes in insulin and glucose were not reported (Larsen et al., 2000).

It is not surprising that an insulin-sensitising effect is more easily detectable than an anti-obesity effect. Stimulation of fat oxidation may rapidly lower the intracellular concentration of metabolites, such as fatty acyl CoA and diacylglycerol that modulate insulin signalling (Laybutt et al., 1999; Idris et al., 2001). The anti-obesity effect, by contrast, must develop gradually as large stores of fat are oxidized (Fig. 3).

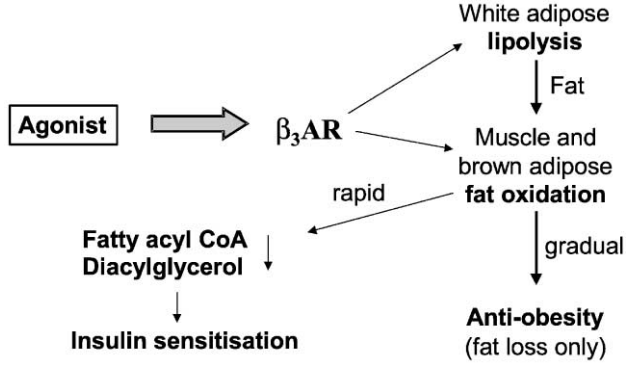

Fig. 3. Why does the insulin-sensitising effect of a β_3-adrenoceptor agonist appear before the anti-obesity effect?

4. Status report

The attraction of β_3-adrenoceptor agonists as potential drugs for the treatment of obesity and Type 2 diabetes is plain to see. The difficulties of producing a compound with good efficacy, selectivity and pharmacokinetic properties suitable for stimulation of the small numbers of β_3-adrenoceptor present in man have, however, defeated a number of pharmaceutical companies. Recent interest has been evident from Merck, from where there have been a number of publications, but an abstract describing the failure of L-796568 to stimulate metabolic rate after 28 days dosing suggests that this compound has been abandoned (Larsen et al., 2000).

Meanwhile, Eli Lilly has presented encouraging Phase 1 data on LY-377604 (Miller et al., 1999) and are believed to be active with this or another compound. Other companies known to have compounds in the clinic are Takeda with the Dianippon compound 2-(3-(7-carboxymethoxyindol-3-yl)-(2*R*)-2-propylamino)-(1*R*)-1-(3-chloro-phenyl)ethanol (AD-9677) (Kato et al., 1998) and GlaxoSmithKline. We must hope that one of these compounds fulfills the promise shown by β_3-adrenoceptor agonists in rodents.

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