SUMMARY - 
Beta₃-adrenoceptor (β₃-AR) agonists were found to have remarkable anti-obesity and anti-diabetic effects in rodents shortly after their discovery in the early 1980s. Despite these promising qualities, several pharmaceutical problems and theoretical concerns have slowed the development of these products as therapeutic agents in humans during the last 15 years. To date, the pharmaceutical industry has not been successful in developing a β₃-AR agonist for use in the treatment of human obesity and type 2 diabetes. Pharmaceutical problems in this area concern important differences between rodent and human β₃-AR, and the difficulty in finding a compound with sufficient bioavailability that is a highly selective and full agonist at the human receptor. Some of these problems seem to have been solved with the cloning of the human β₃-AR, which has made it possible to develop novel compounds directly and specifically against the human receptor. However, several theoretical concerns still remain. These include the major question as to whether the number of biologically active β₃-ARs in adult humans is sufficient to produce relevant metabolic effects, and, if so, whether their long-term stimulation is safe and free of unwarranted side effects. In addition, the mechanisms of action of β₃-AR agonists remain poorly understood. Recent studies using CL 316,243, a highly selective β₃-adrenergic compound, have provided new insights into the potential mechanisms of action of these drugs in rodents as well as the first evidence that treatment with a highly selective β₃-AR agonist exerts relevant metabolic effects in humans. It appears that chronic β₃-adrenergic stimulation in white adipose tissue increases the expression of newly discovered mitochondrial uncoupling proteins (UCP 2 and 3) and a "reawakening" of dormant brown adipocytes. In addition, β₃-ARs may be present in skeletal muscle where ectopic expression of UCP1 has been reported. If these findings are confirmed, tissues other than brown fat may play an important role in mediating β₃-adrenergic effects on thermogenesis and substrate oxidation. In humans, treatment with CL 316,243 for 8 weeks, in spite of limited bioavailability, induced marked plasma concentration-dependent increases in insulin sensitivity, lipolysis, and fat oxidation in lean volunteers, without causing β₁,- or β₂-mediated side effects. These results clearly indicate that favourable metabolic effects can be achieved by selective β₃-AR stimulation in humans. The compounds of the next generation currently emerging from preclinical development are full agonists at the human β₃-AR. These agents have demonstrated promising results in non-human primates. It will be interesting to see whether their efficacy in clinical trials is superior to that achieved with previous (rodent) β₃-AR agonists and, if so, whether their effects will eventually translate into weight loss and improved metabolic control that could facilitate their use as effective drugs for the treatment of obesity and Type 2 diabetes in humans. Diabetes & Metabolism 1999, 25, 11-21

Key-words: β₃ adrenoreceptor, β₃ adrenoreceptor agonist, brown adipose tissue, obesity, type 2 diabetes, treatment.
third “atypical” beta-adrenergic receptor, now referred to as beta_3-AR (β_3-AR), was identified by Arch et al. [1, 2] in the early eighties. It was found that stimulation of this receptor by selective agonists produced remarkable anti-obesity and anti-diabetic effects in rodents [2-8]. This led to a search for β_3-AR agonists for use in human disease [9-20]. Optimism was apparent in 1989 when the gene encoding the human β_3-AR was cloned [21] and later found to be expressed in various human tissues [22, 23]. Unfortunately, the results of human trials over the last 15 years with earlier β_3-adrenergic compounds have been disappointing. Effects on white adipose tissue (WAT) lipolysis, metabolic rate and insulin sensitivity have only been modest, if present at all [9-20]. Furthermore, these non-selective agonists often stimulated β_1- and/or β_2-ARs as well, causing unacceptable side effects such as tachycardia or tremors [24-26] and uncertainty as to whether the observed metabolic effects were actually the result of β_3-AR stimulation. It is now recognized that β_3-adrenergic compounds need to be full and highly selective agonists, specifically targeted to human β_3-AR and such agents are currently under development. However, despite this progress, theoretical concerns persist regarding the pharmacological concept of β_3-AR stimulation in humans. An important unanswered question is whether functionally active β_3-AR are expressed in sufficient amounts in humans to produce the desired metabolic effects. Moreover, in the absence of large amounts of brown adipose tissue (BAT), the mechanisms by which β_3-adrenergic agents could exert their metabolic effects in humans remain unclear.

Recent studies using the highly selective compound CL 316,243 have provided new insights into the mechanisms of action of these drugs in rodents [27-36] as well as the first evidence that selective β_3-AR stimulation exerts metabolic effects in humans [37, 38]. It is the aim of this paper to review. These new findings and the more recent developments in the field.

### Anti-obesity and anti-diabetic effects of β_3-AR agonists in rodent models of obesity and type 2 diabetes, respectively.

<table>
<thead>
<tr>
<th>Anti-obesity effects</th>
<th>Anti-diabetic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mobilization of fat from WAT depots (lipolysis)</td>
<td>Increase in insulin secretion (acute, transient effect)</td>
</tr>
<tr>
<td>Increased BAT-mediated thermogenesis</td>
<td>Improvement in insulin-mediated glucose uptake – due to non-oxidative glucose disposal</td>
</tr>
</tbody>
</table>

| Weight loss – without decrease in food intake | Improved metabolic control – hyperglycemia ↓ |
| selective reduction in body fat | hyperinsulinemia ↓ |
| preservation of fat-free mass | hyperlipidemia ↓ |

**TABLE I.** Anti-obesity and anti-diabetic effects of β_3-AR agonists in rodent models of obesity and type 2 diabetes, respectively.

WAT = white adipose tissue, BAT = brown adipose tissue.
functional BAT [52]. Apparently, the lack of β3-ARs is compensated by β1- and/or β2-ARs in these animals.

In addition to weight loss, β3-AR agonists exert potent anti-diabetic effects in rodent models of Type 2 diabetes (Table I). Chronic treatment reduces, or even corrects, hyperglycaemia, hyperinsulinaemia and hyperlipidaemia in these animals [4, 6, 7, 36]. These effects appear to be independent of the anti-obesity effects of the drugs since they occur at doses not causing a reduction in body weight [14]. The mechanisms underlying the anti-diabetic effect of β3-AR agonists are not fully understood. Administration of β3-AR agonists increases insulin secretion acutely [53], but this effect is transient and of questionable relevance since β3-ARs have not been detected in the pancreas. More likely, the glucose-lowering effect of β3-AR agonists is mediated through improved peripheral insulin sensitivity. The chronic administration of β3-AR agonists increases insulin-stimulated glucose uptake in rodents [4, 6, 7, 35, 36]. It is not certain which tissues are responsible for this effect. Most studies have failed to demonstrate β3-AR mRNA in skeletal muscle, the major contributor to insulin-stimulated glucose uptake [54, 55]. However, others have reported a direct effect of β3-AR agonists on skeletal muscle glucose utilization [56, 57]. Alternatively, in diabetic rodents, the observed increase in skeletal muscle glucose uptake could be secondary to lowered plasma concentrations of FFA (e.g. via the Randle effect) [14, 36, 58], or glucose [36], or both.

ANTI-OBESSION AND ANTI-DIABETIC EFFECTS OF β3-AR AGONISTS IN HUMANS

The promising effects of β3-AR agonists in rodents have led to intensive research to discover β3-adrenergic agonists for the treatment of obesity and Type 2 diabetes in humans [9-20], and several compounds have been tested in humans over the past 15 years [9-13] (Table II). Unfortunately, none of these relatively short studies has demonstrated strong enough effects to encourage further development and marketing. Treatment of obese subjects with BRL 35135 or BRL 26830A, two early compounds from Smith Kline Beecham, had no effect on thermogenesis or fuel metabolism [9, 10]. Ro 40-2148, a β3-adrenergic compound from Roche, induced a marginal (4 %) increase in glucose-induced thermogenesis in obese women, but resting metabolic rate remained unaffected [11]. Equally limited effects of β3-AR ago-
nists were seen in lean subjects [12]. To some extent, more positive results have been obtained regarding the anti-diabetic effects. Several studies have demonstrated an improvement in oral glucose tolerance and a decrease in fasting plasma insulin following treatment with these earlier agonists [9, 10]. In a randomised controlled euglycaemic glucose clamp study [13], BRL 26830A increased insulin-stimulated glucose uptake via stimulation of glucose storage [13], a finding consistent with the effects in rodents [35]. However, neither BRL 26830A nor any of the other compounds was highly \( \beta_3 \)-selective. Since improved insulin action can also be achieved with \( \beta_3 \)-AR agonists [59], it cannot be concluded from these studies that the observed anti-diabetic effects resulted from \( \beta_3 \)-AR stimulation. The common side effects of these compounds in humans were tachycardia and tremors [24-26], indicating a lack of \( \beta_3 \)-selectivity.

As a result of the experience gained in these early trials, several criteria are now recognized as important to the development of \( \beta_3 \)-AR agonists as putative anti-obesity and/or anti-diabetic drugs in humans (Table III).

Firstly, any therapeutic use of \( \beta_3 \)-AR agonists in humans requires a sufficient amount of biologically active \( \beta_3 \)-ARs in target tissues. In rodents, \( \beta_3 \)-AR are abundantly expressed in WAT and BAT [16, 17], key tissues for energy storage and expenditure, respectively. In humans, \( \beta_3 \)-ARs are abundant in BAT, but not in WAT, where only modest amounts of \( \beta_3 \)-AR mRNA have been detected [22]. The physiologic role of BAT in humans, however, is debatable. Newborn infants, who possess relatively large amounts of BAT, are nearly able to double their energy expenditure in response to rather mild cold exposure [60], suggesting an important thermoregulatory role for BAT. With increasing age, however, the amount of BAT in humans decreases [42], so that it has been argued that the amount of BAT, and thus the expression of \( \beta_3 \)-AR in adult humans, may be insufficient to produce satisfactory metabolic effects by \( \beta_3 \)-AR agonists. On the other hand, there is evidence that BAT can be restored in humans by chronic adrenergic stimulation, as demonstrated in patients with phaeochromocytoma and hibernoma [61-63], and to a lesser extent in outdoor workers [64]. Similarly, (rodent) \( \beta_3 \)-AR, in contrast to \( \beta_1 \) and \( \beta_2 \)-ARs, seems to be up- rather than down-regulated by chronic stimulation [53, 65, 66], which can be explained by the lack of phosphorylation sites at its intracellular domain. If the same holds true for human \( \beta_3 \)-AR, treatment with \( \beta_3 \)-AR agonists may require some time until sufficient amounts of \( \beta_3 \)-ARs and BAT have been induced to exert maximum pharmacological activity. For obese and/or diabetic subjects, this could be of particular importance since the impaired thermogenic response to cold exposure observed in these subjects may indicate an impaired BAT- and/or \( \beta_3 \)-AR function [42, 67].

With respect to the compound itself, several factors are important. To date, all agonists tested in human trials have been developed against rodent \( \beta_3 \)-AR. After cloning of the human \( \beta_3 \)-AR [21], however, it became apparent that its pharmacology differed in several important respects from that of the rodent receptor [14, 68, 69]. This led to the recognition that future compounds need to be directed specifically against the human rather than the rodent \( \beta_3 \)-AR. Moreover, none of the previously tested compounds

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**Table II. Overview of results obtained in previous small clinical trials, with earlier, non-selective \( \beta_3 \)-AR agonists in humans.**

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Compound</th>
<th>( \beta_3 )-selectivity</th>
<th>n</th>
<th>Subjects</th>
<th>Duration of treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Mitchell et al. [9]</td>
<td>BRL 35135</td>
<td>unselective</td>
<td>10</td>
<td>Obese, M + F</td>
<td>10 days</td>
<td>improved oral glucose tolerance ↓ glucose storage, ⇔ glucose oxidation ⇔ thermogenesis and body weight</td>
</tr>
<tr>
<td>1994</td>
<td>Haesler et al. [11]</td>
<td>Ro 40-2148</td>
<td>unselective</td>
<td>12</td>
<td>Obese, F</td>
<td>2 weeks</td>
<td>= resting metabolic rate ⇔ fasting plasma glucose, insulin, FFA ↑ glucose induced thermogenesis</td>
</tr>
<tr>
<td>1995</td>
<td>Goldberg et al. [12]</td>
<td>ICI D7114</td>
<td>unselective</td>
<td>16</td>
<td>Lean, M</td>
<td>2 weeks</td>
<td>= 24-h energy expenditure ⇔ substrate oxidation</td>
</tr>
<tr>
<td>1994</td>
<td>Smith et al. [13]</td>
<td>BRL 26830A</td>
<td>unselective</td>
<td>12</td>
<td>Lean, M</td>
<td>10 days</td>
<td>improved insulin sensitivity ↑ glucose storage, glucose oxidation</td>
</tr>
</tbody>
</table>
has been highly β₃-selective, and none has been a full agonist at the human receptor. The lack of β₃-selectivity has not only led to undesired β₁- and/or β₂-mediated side effects, but has also precluded determination of whether the observed effects achieved with these compounds were the result of β₃-AR stimulation. Most previous compounds reached only phase I trials, so that only short-term effects have been tested, often in lean healthy subjects and using metabolic surrogate endpoints. Ultimately, the use of a β₂-AR agonist as an anti-obesity and/or anti-diabetic drug will require that such surrogate effects translate into sustained clinical benefits in patients, namely reduction of body weight and improved glycaemic control. Further important criteria for the development of novel compounds include suitable pharmacokinetic properties – most previous agonists suffered from poor oral bioavailability and/or short plasma half-life – and long-term safety. The latter aspect not only refers to the toxicological profile of a compound itself, but also to the unanswered question as to whether a chronic elevation of metabolic rate by sympathetic stimulation can be safely maintained over months or years.

Several recent achievements in the field should encourage the development of β₃-AR and intensify the search for β₃-adrenergic compounds for use in human disease. These include the potential mechanisms underlying the effects of β₃-AR agonists, the first demonstration of β₃-AR mediated effects in humans, and the development of novel compounds that are specifically directed against human β₃-AR.

### RECENT DEVELOPMENTS

#### Potential mechanisms underlying the action of β₃-AR agonists

Several recent animal studies have further clarified the mechanisms by which β₃-AR agonists exert their anti-obesity and anti-diabetic effects in rodents [27-36].

As far as anti-obesity effects are concerned, the pivotal role of BAT and UCP-1 in the control of energy expenditure and body weight in rodents has been questioned by a recent report indicating that mice lacking UCP-1 were lean and not obese (as had been anticipated) [70]. An additional observation is that treatment with β₃-AR agonists increased the expression of UCP-3 [27] and possibly UCP-2 [71], two newly discovered uncoupling proteins that are expressed not only in BAT but also in other tissues including WAT and skeletal muscle [72-74]. Whether these proteins exert uncoupling activity in humans remains to be proven. However, it is known that as much as 20-40% of the energy expended by all cells in the body (not just brown adipocytes) is used to counter a proton leak down the electrochemical gradient across the inner mitochondrial membrane [75, 76]. In the UCP-1 knock-out mouse, the expression of UCP-2 was up-regulated in BAT, suggesting that UCP-2 may compensate for the lack of UCP-1 [70]. Reitman et al. [27] found that administration of CL 316,243 markedly increased the expression of UCP-3 in WAT. Similar results were recently reported for UCP-2 [71]. If UCP-2 and 3 exerted uncoupling activity, this might mean that WAT (and presumably skeletal muscle) are major contributors to the effects of β₃-AR agonists on thermogenesis and substrate oxidation. Increased expression of the newly discovered UCPs is, however, not the only adaptation induced in WAT by β₃-adrenergic stimulation. Several groups have reported the appearance of brown adipocytes in adipose tissue depots traditionally regarded as WAT following chronic β₃-adrenergic stimulation [28-30]. This finding is in agreement with the detection of UCP-1 expression in these depots following treatment with CL 316,243 [31] and has led to the concept of

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**Table III.** Criteria for the development of novel β₃-adrenoceptor agonists as putative drugs for the treatment of obesity and type 2 diabetes in humans.

<table>
<thead>
<tr>
<th>β₃-AR</th>
<th>β₃-adrenergic compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) developed against human cloned β₁-ARs</td>
<td>1) sufficient amount of biologically active receptors in target tissues</td>
</tr>
<tr>
<td>2) high β₃-selectivity, i.e. – no β₁/β₂-mediated side effects (tachycardia, tremors)</td>
<td>2) no receptor down-regulation following chronic treatment</td>
</tr>
<tr>
<td>3) high activity/potency (full agonist at the human β₃-AR)</td>
<td>3) high activity/potency (full agonist at the human β₃-AR)</td>
</tr>
<tr>
<td>4) clinical efficacy – ↑ insulin action (improved glycemic control)</td>
<td>4) clinical efficacy – ↑ insulin action (improved glycemic control)</td>
</tr>
<tr>
<td>5) suitable pharmacokinetics (incl. sufficient oral bio-availability and plasma half life)</td>
<td>5) suitable pharmacokinetics (incl. sufficient oral bio-availability and plasma half life)</td>
</tr>
<tr>
<td>6) long term safety (including safety of chronic thermogenic stimulation)</td>
<td>6) long term safety (including safety of chronic thermogenic stimulation)</td>
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</tbody>
</table>
“dormant” brown adipocytes in WAT that can be “awakened” by chronic stimulation to exert the full thermogenic capacity of mature brown adipocytes [42]. The capacity to rekindle brown adipocytes in WAT has recently been shown to be a highly variable genetic trait [30] that correlated linearly with the anti-obesity response to treatment with a β3-AR agonist [30]. Whether “dormant” brown adipocytes are present in human WAT and, if so, whether they can be recruited by sustained β3-adrenergic stimulation, remains to be investigated. Another interesting observation was made by Yoshida et al. [31], who reported ectopic expression of functionally active UCP-1 following β3-adrenergic stimulation in skeletal muscle. Clearly, this finding needs to be confirmed, but it is interesting since skeletal muscle, and not BAT, has been found to account for the thermogenic effect of ephedrine, an unsselective sympato-mimetic stimulant, in humans [77]. Other recent studies suggest that β3-adrenergic agonists may exert their anti-obesity effects, at least in part, via effects on food intake and/or expression of the ob gene product leptin, which is thought to act as a satiety factor [32-34]. These two effects, however, appear to be independent of each other. In lean rodents, administration of CL 316,243 acutely inhibited food intake, but this effect was paralleled by a simultaneous 80 % reduction in leptin expression [33]. Furthermore, in the fa/fa rat, an obesity model, hyperphagia due to defective leptin receptors was largely corrected by CL 316,243 without inducing any change in the elevated plasma leptin concentrations in these animals [34]. These results, and others, have led to the recent proposal that brown adipocytes secrete a yet unknown satiety factor other than leptin [78].

The anti-diabetic effects of β3-AR agonists have been further investigated using 2-deoxy-glucose in order to trace the fate of glucose induced by treatment with β3-AR agonists in lean non-diabetic [34] and obese diabetic [35] rats. DeSouza et al. [34] reported that BAT and WAT accounted entirely for the increased glucose disposal brought about by CL 316,243 in normal lean. In contrast, Liu et al. [35] found glucose disposal to be significantly increased in skeletal muscle in obese Zucker diabetic (ZDF) rats treated with CL 316,243. This phenomenon may well have been a secondary effect, however, as CL 316,243 treatment also lowered elevated fasting plasma glucose and free-fatty acid concentrations in these diabetic animals. On the other hand, Cawthorne

![Diagram](image)

**Fig. 2.** Proposed extended concept of putative mechanisms contributing to the anti-obesity and anti-diabetic effects of β3-adrenoceptor agonists. Chronic β3-adrenergic stimulation increases the expression of β3-ARs and induces several adaptations in WAT and skeletal muscle. In WAT, this includes a re-awakening of dormant brown adipocytes, an increase in UCP 2 and -3, and a decrease in leptin expression. β3-ARs may also be expressed in skeletal muscle where they could not only stimulate glucose uptake and storage directly but also induce ectopic expression of UCP-1. If these effects are confirmed, tissues other than BAT may play an important role in mediating the effects of β3-AR agonists on thermogenesis and substrate oxidation.
et al. [79] recently reported preliminary evidence of \( \beta_3 \)-AR expression in skeletal muscle using a monoclonal antibody. These new findings suggest that the theoretical concept of the mechanisms underlying anti-obesity and antidiabetic effects of \( \beta_3 \)-AR agonists may need to be expanded, as suggested in Figure 2.

**Demonstration of metabolic effects of selective \( \beta_3 \)-adrenergic stimulation in humans** – As noted above, the lack of selectivity of previous compounds has led to uncertainty as to whether selective \( \beta_3 \)-adrenergic stimulation in humans can produce the metabolic effects seen in rodent, i.e. 1) improved insulin sensitivity, 2) stimulated fat mobilisation from WAT (lipolysis), 3) increased fat oxidation, and 4) increased energy expenditure (thermogenesis).

We recently reported the first results in humans with CL 316,243, a highly selective \( \beta_3 \)-AR agonist [37]. CL 316,243 belongs to the first generation of compounds developed against the rodent \( \beta_3 \)-AR, but is also a highly selective (and partial) agonist at human the \( \beta_3 \)-AR [77, 78]. In this randomised controlled trial, treatment with CL 316,243 in lean male subjects resulted in a 45% increase in insulin-stimulated glucose disposal (week 4), a 41% increase in plasma free-fatty acid concentrations (week 4 and 8) and a 23% increase in 24-h fat oxidation (week 8). The effects were all linearly related to the achieved plasma concentrations of the drug (right panels) and not accompanied by \( \beta_1 \)-and/or \( \beta_2 \)-mediated side effects. Insulin action was assessed by euglycaemic glucose clamps and energy expenditure and substrate oxidation measured in a respirator chamber (Ref. 37).
effects were all linearly related to the achieved plasma concentrations of the compound (Fig 3) and not accompanied by \( \beta_1 \)- or \( \beta_3 \)-AR-mediated side effects. These results clearly indicate that the expression of \( \beta_3 \)-ARs is sufficient in humans, at least in young lean subjects, to allow relevant metabolic effects by selective agonists. Secondly, marked effects on lipolysis and fat oxidation were achieved after 8 weeks, which suggests that sustained treatment with the \( \beta_3 \)-AR agonist did not result in a significant down-regulation of \( \beta_3 \)-ARs. Thirdly, the effects were much more pronounced in those subjects in whom the highest CL plasma concentrations were achieved, suggesting that even greater effects may be obtained if the oral bioavailability of \( \beta_3 \)-AR agonists can be improved. On the other hand, no effects on energy expenditure or body weight were seen in this study. Moreover, it is not clear how improved insulin action could be achieved in the face of increased FFA concentrations. In another study with CL 316,243, 3 months of treatment increased lipolysis in upper body obese subjects, again, with no effects on body weight [38].

Despite positive metabolic effects, CL 316,243 is no longer under clinical development. As noted above, it was developed against rodent receptor, and it suffered from poor oral bioavailability. Nevertheless, the results with this compound in both rodents and humans should encourage the development and clinical testing of novel agonists developed against the human \( \beta_3 \)-AR.

**Development of novel compounds against the human \( \beta_3 \)-AR** — Soon after significant differences in the pharmacology of human, as compared to rodent, \( \beta_3 \)-ARs were recognized [14, 66, 67], pharmaceutical companies began using the human receptor to develop more specific \( \beta_3 \)-AR agonists. Screening strategies employing cloned human \( \beta_1 \), \( \beta_2 \), and \( \beta_3 \)-AR, which are stably expressed in Chinese hamster ovary (CHO) cells, led to the discovery of several novel compounds that are highly selective for human \( \beta_3 \)-AR [82-87]. To date, no studies in humans with this second generation of agonists have been published, although results in non-human primates appear promising [82-84]. Acute administration of L-755,507, a highly potent human \( \beta_3 \)-selective benzene-sulphonamide agonist developed at Merck, markedly stimulated lipolysis and metabolic rate in rhesus monkeys, whereas chronic treatment increased BAT UCP-1 expression in these animals [82]. However, L-755,507 shows poor bioavailability due to presystemic glucuronidation, and is only a partial agonist at human \( \beta_3 \)-ARs. Quite recently, preliminary data have been presented on L-771,047, a pyridine-ethanolamine with improved bioavailability that is a full and highly selective agonist at the human \( \beta_3 \)-AR [83]. Beecham has developed several novel human \( \beta_3 \)-AR agonists of both the phenyl-ethanolamine and the aryloxypropanolamine class that elicit nadolol-resistant stimulation of lipolysis in vitro [49, 86]. These studies have revealed that stimulation of human cloned \( \beta_3 \)-AR predicts whether or not compounds will elicit lipolytic activity in vitro in human white adipocytes, but have also shown that it is difficult to predict from studies on cells transfected with cloned \( \beta \)-ARs which \( \beta \)-ARs will mediate responses in tissues [50]. A useful tool for in vivo testing of such novel compounds may be the recently developed \( \beta_3 \)-AR knock-out mouse in which genomic sequences of human \( \beta_3 \)-AR have been introduced transgenically [88].

Whether the improved pharmacological properties of novel human \( \beta_3 \)-adrenergic agonists will translate into more satisfactory results in human clinical trials remains to be seen. Clinical testing of this second generation of agents should include studies to clarify the mechanisms of action of \( \beta_3 \)-AR agonists (such as by including fat and muscle biopsies) as well as long-term investigations to assess the chronic effects of \( \beta_3 \)-AR stimulation in humans. Intensified research efforts have recently led to two other major achievements in this field. One is the development of the first selective \( \beta_3 \)-AR antagonists [89, 90], which should serve as excellent tools for the study of \( \beta_3 \)-AR physiology and pharmacology. The other relates to accumulating evidence for the existence of a putative "\( \beta_3 \)-AR", the expression of which has already been demonstrated in humans [91-94]. The physiological role of this receptor remains to be elucidated, but its major function appears to lie in cardiac rather than metabolic regulation.

## CONCLUSIONS

More than 15 years after the discovery of the first \( \beta_3 \)-AR agonists and the recognition of their anti-obesity and anti-diabetic effects in rodents, the therapeutic potential of \( \beta_3 \)-AR agonists in humans is still uncertain. However, important achievements have been made in recent years, re-intensifying the search for \( \beta_3 \)-AR agonists that prove effective in humans. These include new insights into the mechanisms of action of these agents in rodents, the first demonstration that selective \( \beta_3 \)-AR stimulation elicits metabolic effects in humans, and the development of a second generation of compounds that are full and highly selective agonists at the human \( \beta_3 \)-AR. Further studies are needed to clarify the mechanisms underlying the effects of \( \beta_3 \)-AR agonists in humans and to elucidate whether more satisfactory results can be achieved with these novel compounds, so that effective drugs could eventually be developed for the treatment of human obesity and Type 2 diabetes.

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We are pleased to announce that the Zagreb Diabetology School Vuk Vrhovac will accept nominations for the 1998 Vuk Vrhovac Essay Award.

The aim of the Vuk Vrhovac Award is to stimulate the exchange of new ideas and research leading to prevention, detection, treatment and cure of diabetes and its complications. The award will be given for the best original paper which most significantly advances our understanding of the etiology of diabetes and its complications or shows how these can be reduced in accordance with the St. Vincent Declaration principles. Nominations will be accepted for either basic or clinical biomedical research in diabetes. More than one researcher may be nominated if they have worked as a team.

Winners of the Vuk Vrhovac Essay Award will be decided by the Advisory Board of international experts whose decision is final.

The prize of 2,000 DM and a diploma will be awarded at a ceremony held on the occasion of the Croatian Diabetology Day in Zagreb in June 1999.

All manuscripts will be considered for publication in Diabetologia Croatica and should be prepared in accordance with the journal’s instructions to authors. The awarded manuscript will be published in Diabetologia Croatica. Other papers nominated for the award will be considered for publication using a standard procedure.

Nominations should be sent by March 31, 1999 to:

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