Editorial

The notion that "atypical" β-adrenergic receptors (β-ARs) might exist originated with observations that a major component of β-agonist–mediated lipolysis in rodent white and brown adipose tissue resisted blockade by β-antagonists (1). Further evidence for the existence of distinct atypical β-ARs followed the synthesis of new β-agonists which potently stimulated lipolysis and energy expenditure in brown adipose tissue (BAT), while having little or no effect on β_1- or β_2-AR–mediated processes (1). The molecular target for atypical β-agonists was revealed with the cloning and characterization of a gene encoding the human β_3-AR (2). Homologous genes in rat and mouse have also been isolated. RNA encoding the β_3-AR is expressed in white and brown adipose tissue and in the gastrointestinal tract. Pharmacologic characterization of cell lines expressing recombinant receptors has revealed that cloned β_3-ARs are resistant to blockade by conventional β-antagonists and are potently stimulated by β_3-selective agonists (3). Given that the functionally identified atypical β-AR and the molecularly cloned β_3-AR have similar tissue distributions and pharmacologic profiles, it is generally accepted that they are one in the same. Because of the remarkable ability of β_3-agonists to selectively increase energy expenditure, there has been much interest in these compounds as potential antiobesity drugs. However, many fundamental questions regarding β_3-ARs remain unanswered.

Are β_3-ARs present in human adipose tissue? There has been considerable debate as to whether functionally important numbers of β_3-ARs are present in human adipose tissue. This controversy may in part result from the fact that some fat depots express β_3-ARs while others do not (3). White adipocytes derived from subcutaneous depots express few β_3-ARs and respond minimally or not at all to β_3-selective agonists, while adipocytes derived from intraabdominal or visceral depots express many more β_3-ARs and are responsive to β_3-selective agonists. β_3-ARs are apparently expressed in human BAT as well (3).

What is the role of β_3-ARs in physiology and pathophysiology? Little is known about the role of β_3-ARs in normal physiology. In this issue of *The Journal,* Lonnqvist et al. (4) provide evidence that visceral adipocytes obtained from individuals with upper body obesity have increased lipolysis in response to catecholamines and that this is mediated, in large part, by an increase in β_3-AR function. Since the venous drainage of visceral adipocytes is into the portal vein, this might lead to increased delivery of free fatty acids to the liver of obese individuals, thus exacerbating hepatic insulin resistance. Further investigation will be required to determine if this finding represents a link between upper body obesity and insulin resistance.

A provocative study, recently presented in abstract form (5), reported that a missense mutation in codon 64 of the β_3-AR occurs frequently in Pima Indians, known for their high prevalence of obesity and non–insulin-dependent diabetes mellitus. Individuals who possessed this mutation, particularly homozygotes, tended to have reduced metabolic rates, increased body weight, and earlier development of non–insulin-dependent diabetes mellitus. While this finding raises the possibility that human β_3-ARs are functionally important, further information on this observation will be required to determine its true significance. Using homologous recombination, we have recently generated mice which lack the β_3-AR. Evaluation of these animals will likely be informative with regards to the physiologic role of this receptor (6).

Is the human β_3-AR a genuine target for antiobesity drugs? β_3-selective agonists are candidate antiobesity drugs because of their profound ability to increase energy expenditure and improve glucose homeostasis in obese rodents (1). This activity is likely to be mediated by stimulation of BAT, a tissue with enormous capacity for energy expenditure. In rodents, BAT is thought to be functionally important. It is dysfunctional in genetic models of obesity in which decreased thermogenesis is seen, and transgenic mice engineered to have decreased BAT are obese (7). In contrast to rodents, humans clearly have less BAT. While there is general agreement that human BAT expresses β_3-ARs (3), there is significant debate as to whether humans have sufficient BAT to mediate physiologically meaningful responses to β_3-agonists. Chronic treatment with β_3-agonists causes marked hypertrophy of BAT in rodents and dogs. Clinical trials with highly selective β_3-agonists may determine whether humans are capable of a similar response. If so, this class of drugs could have important therapeutic potential in obesity and obesity-linked diabetes.

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References

1. Arch, J. R. S., and A. J. Kaumann. 1993. β_3 and atypical β-adrenoceptors. *Med. Res. Rev.* 13:663–729.

2. Emorine, L. J., S. Marullo, M.-. Briend-Sutren, G. Patey, K. Tate, C. Delavier-Klutchko, and A. D. Strosberg. 1989. Molecular characterization of the human β_3-adrenergic receptor. *Science (Wash. DC).* 245:1118–1121.

3. Emorine, L., N. Blin, and A. D. Strosberg. 1994. The human β_3-adrenoceptor: the search for a physiological function. *Trends Pharmacol. Sci.* 15:3–7.

4. Lönnqvist, F., A. Thörne, K. Nilsell, J. Hoffstedt, and P. Arner. 1995. A pathogenic role of visceral fat β_3-adrenoceptors in obesity. *J. Clin. Invest.* 95:1109–1116.

5. Walston, J., K. Silver, S. Austin, F. S. Celi, N. Rabin, C. Bogardus, W. C. Knowler, J. Roth, and A. R. Shuldiner. 1994. Identification of a missense mutation in the beta 3-adrenergic receptor gene: potential relevance to obesity and NIDDM in Pima Indians. Satellite Conference of the International Congress on Obesity (Abstr.).

6. S-Susulic, V., J. A. Lawitts, J. S. Flier, and B. B. Lowell. 1994. Germ-line transmission of a disrupted β_3-adrenergic receptor gene following microinjection of DNA into mouse zygotes. *J. Cell. Biochem. Suppl.* 18A:172*a*. (Abstr.)

7. Lowell, B. B., V. S-Susulic, A. Hamann, J. A. Lawitts, J. Himms-Hagen, B. B. Boyer, L. P. Kozak, and J. S. Flier. 1993. Development of obesity in transgenic mice after genetic ablation of brown adipose tissue. *Nature (Lond.).* 366:740–742.

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