The potential significance of $\beta_3$ adrenergic receptors

The notion of "atypical" $\beta$-adrenergic receptors ($\beta$-ARs) might exist originated with observations that a major component of $\beta$-agonist-mediated lipolysis in rodent white and brown adipose tissue resisted blockade by $\beta$-antagonists (1). Further evidence for the existence of distinct atypical $\beta$-ARs followed the synthesis of new $\beta$-agonists which potentely stimulated lipolysis and energy expenditure in brown adipose tissue (BAT), while having little or no effect on $\beta_1$- or $\beta_2$-AR-mediated processes (1). The molecular target for atypical $\beta$-agonists was revealed with the cloning and characterization of a gene encoding the human $\beta_3$-AR (2). Homologous genes in rat and mouse have also been isolated. RNA encoding the $\beta_3$-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 $\beta_3$-ARs are resistant to blockade by conventional $\beta$-antagonists and are potentely stimulated by $\beta_3$-selective agonists (3). Given that the functionally identified atypical $\beta$-AR and the molecularly cloned $\beta_3$-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 $\beta_3$-agonists to selectively increase energy expenditure, there has been much interest in these compounds as potential antiobesity drugs. However, many fundamental questions regarding $\beta_3$-ARs remain unanswered.

Are $\beta_3$-ARs present in human adipose tissue? There has been considerable debate as to whether functionally important numbers of $\beta_3$-ARs are present in human adipose tissue. This controversy may in part result from the fact that some fat depots express $\beta_3$-ARs while others do not (3). White adipocytes derived from subcutaneous depots express few $\beta_3$-ARs and respond minimally or not at all to $\beta_3$-selective agonists, while adipocytes derived from intraabdominal or visceral depots express many more $\beta_3$-ARs and are responsive to $\beta_3$-selective agonists. $\beta_3$-ARs are apparently expressed in human BAT as well (3).

What is the role of $\beta_3$-ARs in physiology and pathophysiology? Little is known about the role of $\beta_3$-ARs in normal physiology. In this issue of The Journal, Lonngqvist 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 $\beta_3$-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 $\beta_3$-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 $\beta_3$-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 $\beta_3$-AR. Evaluation of these animals will likely be informative with regards to the physiologic role of this receptor (6).

Is the human $\beta_3$-AR a genuine target for antiobesity drugs? $\beta_3$-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 $\beta_3$-ARs (3), there is significant debate as to whether humans have sufficient BAT to mediate physiologically meaningful responses to $\beta_3$-agonists. Chronic treatment with $\beta_3$-agonists causes marked hypertrophy of BAT in rodents and dogs. Clinical trials with highly selective $\beta_3$-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