INVITED COMMENTARY

Obesity and diabetes and the beta-3 adrenergic receptor

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The article by Umekawa et al. in this issue of the Journal (1) highlights a remarkable anti-obesity and anti-diabetic effect of the selective beta-3 adrenergic receptor (B3-AR) agonist, CL316,243, in a rat model of obesity and non-insulin-dependent diabetes mellitus. Treatment was accompanied by increased brown adipocyte contents of uncoupling protein (UCP) mRNA and protein, the specialized brown fat (BAT) mitochondrial protein responsible for uncoupling oxidative phosphorylation and generation of heat, and GLUT mRNA and protein, the glucose transporter responsible for the facilitated transport of glucose into this tissue. In addition, the paper contributes to the discussion about whether the appearance of UCP in areas traditionally considered white fat (WAT) reflects the recruitment of dormant BAT intermixed amongst mature WAT cells or the conversion of WAT into BAT cells. These observations and the question as to whether B3-AR agonists, which so effectively reverse obesity and diabetes in rodents, can also correct human conditions deserve comment.

BAT and thermoregulation

For years, BAT was thought to exist exclusively in hibernating animals. Evidence for its role in thermoregulation was first presented in 1963 and unequivocally confirmed in 1978. Evidence of its link to obesity was first suggested in experiments by Rothwell and Stock using their 'cafeteria' model of overfeeding. This observation received important support when Landsberg and Young who, contrary to intuition at the time, discovered that sympathetic nervous system activity which was known to control cold-induced BAT thermogenesis was increased by overfeeding and decreased by underfeeding. Since a defective thermogenic response to cold had been observed in several rodent models of obesity, Himms-Hagen (2) suggested that obesity in humans might result from a similar pathology. These discoveries, coupled with the observed resistance to weight gain during overfeeding in lean volunteers in the Vermont Studies of Obesity, and more recently the relatively low metabolism in reduced obese humans at Rockefeller University, lend support to the idea that the relative ease of weight gain of some individuals, which has led to an epidemic of obesity in modern societies, might be related to variations in the amount or function of BAT.

BAT and obesity

Much has been learned about the function of BAT in rodents. It is clear that the heat produced in BAT plays a critical role in the ability of small mammals to survive in the cold, and that exposure to cold is associated with hypertrophy and hyperplasia of BAT, including an increase in mitochondrial density, UCP and GLUT 4 content of BAT. Cold exposure also leads to increased caloric intake, but no abnormal gain in weight. Genetically obese rodents become obese when raised in the warm, but die in the cold in spite of increased caloric intake, a result of their defective BAT thermoregulatory response. Genetically obese rodents are 'easy gainers' in response to 'cafeteria' high fat diets, while the response in other strains of rats is quite variable (3). Therefore, as revealed by the Vermont Studies in humans, there are 'easy and hard gainers' amongst rats as well. Except for the 'easy gainers', it is sometimes difficult to determine with certainty whether the obesity results from a deficit in BAT thermogenesis, increased caloric intake or a combination of the two; although there is increasing evidence that variability in the amount or responsiveness of BAT plays a role (4, 5). Loss of weight without a significant change in energy intake is clearly demonstrated in the accompanying article and others in which obesity is shed when B3-AR agonists are administered to obese and older animals. Younger leaner animals become relatively leaner in response to treatment although continue to match energy intake to expenditure better than older obese animals, reminiscent of their ability to also match intake with expenditure in the cold better than the obese.

Molecular gymnastics in BAT

If sufficient metabolically intact BAT is required for the normal response to cold, the same should hold if BAT plays a role in the sensitivity to gain in weight in response to high energy intakes. Several interesting molecular biologic approaches have been used to examine this issue. The first was to test if intact BAT was truly important in diet-induced obesity by producing a mouse without functioning BAT (6). As expected, mice lacking BAT developed obesity, but they also became hyperphagic like the genetically obese models, making it unclear if the obesity was secondary to the...
caloric efficiency or increased caloric intake or both. Raising these mice at warmer (thernoneutral) temperatures prevents both the obesity and hyperphagia, emphasizing the importance of ambient temperature in the mismatching of intake and expenditure and suggesting that BAT plays a role in regulating energy intake as well as energy expenditure (7).

Several other molecular gymnastic approaches have clarified and confused this issue. When the B3-AR is knocked out, although resistant to stimulation by B3-AR agonists, the mice tolerate cold and gain only a modicum of weight (8). These mice do, however, overexpress B1-ARs in their BAT, and it is known that overexpression of B1-ARs can result in the appearance of brown adipocytes in WAT and in resistance to diet-induced obesity (9). It should be kept in mind that, except for the neuropeptide Y (NPY) knockout in ob/ob mice mentioned below, these transgenic models are imposed in normal lean mice and, when normal, these mice only become obese if they are overfed. Again, this is not the case in genetically obese mice, where the deficit in BAT thermogenesis unquestionably plays an important role in their obesity. These observations become even more interesting when several additional transgenic models are considered. When UCP itself is knocked out, these UCP-deficient mice, although extremely sensitive to cold and unresponsive to B3-AR agonists, unlike the BAT-less mice described earlier do not become obese. While cold-intolerant, as is the genetically obese mouse, the UCP-knockout mouse is neither hyperphagic nor obese. These mice do, however, overexpress the newly discovered UCP homolog, UCP2, in their BAT which perhaps compensates for the absence of UCP1 (10, 11). However, when UCP is overexpressed, including ectopically in WAT (12–14), or when the regulatory subunit II of protein kinase A is knocked out and is spontaneously replaced by the more cyclic AMP-responsive regulatory subunit I (15, 16), the animals resist obesity and the fat stores of lean mice are not depleted, suggesting some dietary compensation to their hypermetabolic states. Even more interesting is the energy intake of mice in which NPY, the putative leptin-associated neuromodulator of satiety, is knocked out. While deleting NPY in normal lean mice caused no change in energy intake or expenditure or body weight, deleting NPY in obese (ob/ob) leptin-deficient mice resulted in decreased intake and loss of weight. Their energy expenditure, although lower than the ob/ob mouse relative to body weight, was probably unchanged relative to their lean body masses (17, 18).

It is difficult to draw a clear or consistent conclusion from these studies. However, taken together they suggest that (a) lean and spontaneously obese rodents respond with different sensitivities to high fat diets, exposure to cold and certain molecular genetic manipulations, (b) energy intake and expenditure are more nearly matched in lean than obese rodents at any temperature, and (c) BAT plays a more important role than previously assumed in regulating energy intake, either secondary to its release of heat (thermoregulatory feeding) or by secreting a satiety factor. The tight link between peripheral and central satiety factors and thermogenesis in BAT is further emphasized by the discovery that leptin stimulates thermogenesis in BAT through central efferent sympathetic nerves (19), and B3-AR agonists suppress adipocyte leptin synthesis and secretion (20, 35). It will be interesting to see where all of this leads.

**BAT and diabetes**

Administration of B3-AR agonists normalizes both plasma insulin and glucose in diabetic rodents and has little, if any, effect on these parameters in lean animals. The effect is independent of change in weight. The mechanism(s) responsible for this are not clear. When initially administered, B3-AR agonists produce a striking increase in plasma insulin concentrations. This response is sustained, consistent with the lack of B3-ARs in the pancreas. This acute insulin response is absent in mice lacking B3-ARs and is restored when these receptors are replaced in both WAT and BAT, but not when replaced in BAT only (21). The correction of the diabetes following treatment with B3-AR agonists is thought to result from a reduction in the Randle fatty acid effect and loss of weight; however the correction of the hyperglycemia takes place before significant loss of weight. Recent studies have traced the fate of glucose in response to B3-AR agonists to determine which tissues were responsible for the improved blood glucose and insulin sensitivity. These studies, quite surprisingly, have found that the greatest increase in glucose uptake in response to B3-AR agonists is into fat, and not muscle as expected, emphasizing a direct and more important role of the fat organ in carbohydrate metabolism than previously suspected. The improved peripheral insulin sensitivity was also accompanied by improved insulin suppression of hepatic glucose output (22, 23, CJ de Souza, MF Hirshman & ES Horton, personal communication).

The question now is to understand the fate of this glucose. BAT is by weight the most potent de novo lipogenic tissue in the body. The purpose of BAT is to produce heat; therefore converting glucose into fatty acids before their oxidation makes sense, since this is an energy-wasteful heat-producing metabolic pathway. There are, however, theoretical reasons why this should not be an important pathway for the disposal of glucose, but this should be tested. Direct oxidation of the glucose is also likely, but this would compete with the oxidation of fatty acids which are the primary fuel for BAT as reflected by the decline in respiratory quotient which accompanies BAT stimulation. For these and other reasons the most likely fate of most of the glucose taken up into WAT and BAT is metabolism to lactate. This would create a cycle between fat and the
liver similar to the Cori cycle between muscle and liver (24). However, unless simultaneously associated with decreased caloric intake, it is still not entirely clear why B3-AR agonists lower glucose and improve insulin sensitivity in rodents. There are reports that B3-AR agonists increase glucose uptake into muscle (25, 26). However, in the absence of B3-ARs in muscle and barring the discovery of another receptor to which these agonists bind, it is difficult to understand how selective B3-AR agonists could be responsible for this effect.

The accompanying paper (1) reports increased mRNA and protein for GLUT 4 in fat, but not in the muscle of rats treated with CL316,243. This is not surprising since cold exposure, which is mimicked by treatment with B3-AR agonists, does the same. It also supports the recent finding that BAT and WAT are the major reservoirs for the increased disposal of glucose following treatment with B3-AR agonists.

Reactivation of dormant BAT by B3-AR agonists?

This is a controversial issue which is not made easier by the fact that the nuclear material from WAT cells comprises but a small fraction (less than 10%) of the nuclear material of tissues obtained from areas considered WAT. Since UCP is the signature protein of BAT, the question is whether ‘ectopic’ expression of UCP occurs in WAT cells which are converted to BAT cells or whether ‘hidden’ but dormant BAT cells are reawakened by B3-AR stimulation. More work has been done on this issue in rodents (3, 27, 28) than in humans, but a recent article (29) using primary cultures of perinephric fat from humans suggests that B3-AR stimulation reawakens dormant BAT cells in this predominately WAT tissue. It is clear, however, that B3-AR agonists are incapable of stimulating early commitment and differentiation of BAT cells, since B3-AR only appear during the late stages of differentiation where their primary action is to increase, in collaboration with sympathetic nervous system-stimulated local generation of triiodothyronine, the transcription and translation of UCP protein, and therefore the capacity of BAT to generate heat.

Potential for the use of B3-AR agonists for treating obesity and diabetes in humans

There is no question that BAT is present in humans of all ages, and functionally present in human newborn infants who are capable of increasing their resting energy expenditure in response to cold without shivering. There is evidence for functional BAT in adults with pheochromocytomas where, in addition to elevation of blood pressure, loss of weight is a hallmark of the disease, and also in cold-acclimatized individuals. The important question is whether enough BAT can be rekindled by treatment with B3-AR agonists to produce weight loss and/or improved insulin sensitivity, or whether methods may be required to increase the bulk of BAT, such as with peroxisome proliferator-activated receptor γ activators like the thiazolidinediones which are known to stimulate early differentiation of fat cells, including BAT cells (30). The results of the first clinical trials of B3-AR agonists yielded some encouraging results (31, 32). However, these early agonists were not selective or full agonists of the human receptor. The next generation of B3-AR agonists will have been developed against the human B3-AR as selective and full agonists. The success or not of these new B3-AR agonists in treating obesity and diabetes will become evident as these compounds move from safety to efficacy testing in humans. Information from early studies of these new compounds in primates and humans appears promising (33, 34, P Barnett, P Coskeran, C Boulox, W Bradbury, Y Kruszynska & P Boulox, personal communication).

References

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Received 13 February 1997
Accepted 15 February 1997