New peptide-based therapies for metabolic diseases

Nouvelles thérapies à base de peptides

M.D. Culler

Biomeasure Incorporated, IPSEN, 27, Maple Street, Milford, MA 01757, United States

Available online 16 April 2008

The spectrum of metabolic diseases, ranging from wasting disorders at one extreme to obesity and the resulting disease sequelae at the other, constitute one of the greatest areas of unmet medical need. Recent discoveries elucidating roles of several key peptides and their receptors in the physiological regulation of metabolic functions have presented opportunities to develop novel approaches for the management of metabolic diseases. Peptides are excellent target molecules for use in metabolic diseases due to their potential for greater receptor selectivity and, consequently, greater safety than small molecule receptor ligands. One such example is ghrelin, a 28-amino acid peptide discovered as the natural ligand for the growth hormone (GH) secretagogue (GHS) receptor. In addition to the anticipated property of stimulating GH secretion, ghrelin has been demonstrated to induce body weight (BW) gain and to increase food consumption. As a result, ghrelin has received a great deal of attention due to the hope that a GHS antagonist might be useful for inducing weight loss. In our efforts to create analogs of ghrelin, we identified a full-length ghrelin analog, BIM-28163, that binds to the GHS receptor, but is completely inactive; as such, BIM-28163 is a competitive antagonist of ghrelin at the GHS receptor. Tested in vivo, BIM-28163 does not induce GH secretion and completely blocks the ability of ghrelin to stimulate GH secretion; however, BIM-28163 is equally as efficacious as natural ghrelin in stimulating increased BW and food intake. These results suggest that a ghrelin receptor other than the known GHS receptor regulates the effects of ghrelin on BW and feeding. Consequently, we have focused our attention on developing agonist analogs of ghrelin for treatment of cachexia and have used semi-chronic weight gain in vivo as our end point for compound screening, rather than interaction with the GHS receptor. These efforts led to the identification of a novel analog of ghrelin, BIM-28131, which is approximately six times smaller than natural ghrelin with more than 10 times greater circulating half-life. BIM-28131 induces a unique biphasic dose-related response that reaches up to three-fold greater efficacy than natural ghrelin in inducing weight gain and that may suggest a synergistic interaction with more than one ghrelin-interacting receptor. BIM-28131 has also been demonstrated to be highly efficacious in preventing the loss of BW and both lean and fat mass in rodent models of cachexia. In addition, BIM-28131 has been demonstrated to have striking dual anti-inflammatory action, blocking both the release, as well as the action, of pro-inflammatory cytokines. This potent opposition of inflammatory cytokines may allow BIM-28131 to not only maintain body weight and composition through alteration of food intake and nutrient storage, but to inhibit the underlying mediators of cachexia. In another example, focusing on the mechanisms by which food intake and excess weight gain might be inhibited, we have generated peptide agonists based on alpha-MSH that are potent activators of the melanocortin subtype-4 (MC4) receptor. The MC4 system is a well-established central node in the regulation of food intake and energy balance. We have identified an agonist peptide, BIM-22493 with subnanomolar ability to activate the MC4 receptor and that effectively reduces both food intake and BW in normal rodents, as well as in both diet-induced and genetically susceptible rodent models of obesity. Follow-up studies in normal dogs demonstrate that the striking ability of BIM-22493 to reduce food intake and induce weight loss is associated with neither nausea nor with changes in either behavior or activity. In addition, BIM-22493 has been demonstrated to reverse insulin-resistance and to improve circulating lipids in obese rodents. The specificity of BIM-22493 can be fully demonstrated by a complete lack of effect in animals lacking the MC4 receptor. These two peptide analogs, BIM-28131 and BIM-22493, exemplify the tremendous potential for peptide therapeutics in treating the full spectrum of metabolic diseases.

E-mail address: michael.culler@ipsen.com.

0003-4266/$ – see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ando.2008.02.019