OBESITY DRUGS

Illuminating weight loss

Drugs that target the endocannabinoid system by inhibiting the cannabinoid 1 receptor (CB1R) have been shown to reduce body weight. However, the physiological mechanisms by which such drugs achieve this in humans are not fully understood. Heymsfield and colleagues now present data indicating that the CB1R inverse agonist taranabant mediates weight loss in humans by decreasing food intake and increasing resting energy expenditure.

Taranabant has been shown to cause weight loss in rodents when the central nervous system CB1R occupancy is above 30%. To test the hypothesis that the drug would have the same effect in humans, the authors first determined the dose needed to achieve target CB1R brain occupancy. A positron emission tomography study performed using the CB1R-selective ligand [^{18}F]MK-9470 indicated that an average target of 30% occupancy would be reached with taranabant doses of 4–6 mg per day.

Next, they conducted a double-blind, placebo-controlled study to determine whether treatment with taranabant would decrease body weight in obese patients more than treatment with placebo, in conjunction with a reduced-calorie diet. Over 12 weeks, patients receiving taranabant (0.5–6 mg) achieved more weight loss compared with patients receiving the placebo in a dose-dependent manner. The most common adverse events experienced during this study were gastrointestinal- and psychiatric-related.

To investigate the mechanisms underlying the observed weight loss, the authors devised a 24-hour food-intake study (double-blind, placebo- and active-controlled, single-dose, four-period crossover). During this time period, patients treated with taranabant (12 mg to simulate steady-state exposure to a 6 mg chronic dose) reduced their calorie intake compared with those receiving placebo. Further to this, a parallel 24-hour indirect calorimetry study showed that patients receiving taranabant experienced a small increase in energy expenditure (indicating that the basal metabolic rate was raised) accompanied by a significant decrease in respiratory quotient (suggesting an increase in fat oxidation).

An important issue for the future therapeutic potential of CB1R-targeted agents such as taranabant is the clinical significance of psychiatric-related adverse events. These have been a source of concern for the selective CB1R antagonist rimonabant (Acomplia; Sanofi–Aventis), which has received regulatory approval in Europe but not in the US, following a negative FDA advisory committee vote. Results from a Phase III trial of taranabant that could clarify this issue, as well as the extent of its efficacy, are anticipated to be announced later this year.

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ORIGINAL RESEARCH PAPERS Addy, C. *et al.* The acyclic CB1R inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. *Cell Metab.* **7**, 68–78 (2008)
FURTHER READING Cooke, D. and Bloom, S. The obesity pipeline: current strategies in the development of anti-obesity drugs. *Nature Rev. Drug Discov.* **5**, 919–931 (2006)