Current research and developments in pharmacological treatments for obesity

The Journal’s series on science continues this month with an article from Helen Simpson and Mark Ashton that describes current drug treatments for obesity and highlights potential new developments.

Being overweight and obesity represent a rapidly growing threat to the health of populations in an increasing number of countries. In fact, they are now so common that they are replacing traditional problems like under-nutrition and infectious diseases as the most significant causes of ill health.1 The main causes are increased consumption of energy-dense foods, which are high in saturated fats and sugars, and reduced physical activity. Methods to treat obesity include dietary management, physical activity and exercise, and anti-obesity drugs. Gastrointestinal surgery is reserved for extreme cases.

There are four broad areas that provide valid drug targets for the treatment of obesity:2

- The inhibition of nutrient absorption
- The enhancement of peripheral satiety or adiposity signals
- Alteration of metabolic rate or substrate use
- Action at central nervous system targets causing altered energy balance

Agents may have multiple modes of action that include more than one of the above broad mechanisms.

Inhibition of nutrient absorption

The only licensed drug that inhibits nutrient absorption is orlistat, which is available on prescription as Xenical (orlistat 120mg) and over the counter as Alli (60mg). Orlistat is an intestinal lipase inhibitor that reduces the uptake of dietary fat in the intestine. Associated side effects include flatulence, diarrhoea, oily spotting and loose oily stools.

XENDOS (Xenical in the prevention of diabetes in obese subjects) was the first study to demonstrate that an anti-obesity agent can reduce the progression to diabetes when compared with lifestyle changes alone (relative risk reduction of 37 per cent after four years’ treatment), especially in obese patients with impaired glucose tolerance.1 A new drug in this category, cetilistat — claimed to be better tolerated and with fewer side effects than Xenical due to differences in the molecular structures — has completed phase I and II trials in the west and is currently in phase III trials in Japan.

Peripheral satiety and adiposity signals

There is no licensed drug that enhances peripheral satiety or adiposity signals at present. Lorcaserin is a novel agent that was developed by Arena Pharmaceuticals and is a selective serotonin 2C receptor agonist. The serotonin 2C receptor is found in the brain, including the hypothalamus, an area involved in the control of appetite and metabolism. Lorcaserin is reportedly more specific and should therefore have fewer side effects than other drugs of this class, such as fenfluramine, which was previously removed from the market due to an associated increase in the risk of heart valve abnormalities.1 In September 2010, lorcaserin failed to get a recommendation from the US Food and Drug Administration advisory committee, making regulatory approval less likely.

Leptin, an appetite-suppressing hormone secreted by fat tissue, was discovered over a decade ago and gave great hopes for an effective treatment for obesity. But hopes dimmed when it was found that obese people are unresponsive to leptin due to development of leptin resistance in the brain. However, a recent study4 showed that increased endoplasmic reticulum stress and activation of the unfolded protein response (a cellular stress response) in the hypothalamus of obese mice inhibits leptin receptor signalling. It was also shown that chemical chaperones 4-phenyl butyric acid and tauroursodeoxycholic acid, which have the ability to decrease endoplasmic reticulum stress, act as leptin-sensitising agents. When taken together, these results may provide the basis for a novel treatment for obesity.

Neuropeptide Y has been demonstrated to have critical roles in the physiological control of appetite and energy homeostasis.3 Neuropeptide Y stimulates food intake, inhibits energy expenditure, increases body weight and increases anabolic hormone levels by activating the neuropeptide YY(1) and Y(5) receptors in the hypothalamus. Based on these findings, several neuropeptide YY(1)
An increasing awareness of the chronic, multifactorial nature of obesity will, ideally, lead to the development of new, safe and effective long-term treatment programmes.


References

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