

Summaries Wilding: Pharmacotherapy of obesity

Summary

F. Xavier Pi-Sunyer

Why drugs?

Drug therapy for obesity has had a difficult past history. A number of drugs have had addictive or toxic properties that have required discontinuation. Pharmacotherapy for obesity has an important role in those persons who have failed behavioral weight loss attempts or as an adjunct to those attempts. The interest in pharmacotherapy for obesity is an outgrowth of the now general recognition that it is a chronic disease that cannot be cured, but can be treated. Treatment, however, will generally be a life-long affair. The focus on drug therapy is due to the frequent failure of non-pharmacological weight loss programs.

At present, only two drugs, sibutramine and orlistat, are approved for long-term use in the US and in much of the rest of the world. The development of new drugs that could help treatment and prevention is greatly needed. The risk/benefit ratio is important in deciding the usefulness of drugs. Drugs are helpful because the defense of baseline body weight by the body is very forceful, no matter what that baseline weight is. Energy expenditure falls and hunger greatly increases when weight is lost. Because of these very strong and sustained defensive biological reactions to weight loss, maintaining weight loss over time becomes increasingly difficult.

There are a large number of possible agents that could be developed. There are a wide variety of neurotransmitters, gut peptides, and other small molecules that are active in food intake and energy expenditure that can be copied or blocked.

It is probable that in the future, as our knowledge base increases, drugs will be developed that will be useful for some persons and not others, according to their individual genomic make-up. That would usher in an era of personalized medicine in the weight loss field.

It is important to accelerate the development of drugs that are safe and effective. Success in this endeavor could prevent a great deal of disease and improve quality of life.

Summary

George A. Bray

Some historical aspects of drug treatment for obesity

The article describes the often serendipitous discoveries of pharmaceuticals that have been used for the treatment of overweight persons since the late nineteenth century. A recurring theme in the history of obesity drugs is the recognition of unintended consequences that result in the drugs' discontinuation of use.

Keywords: adverse effects, amphetamine, dinitrophenol, fenfluramine/phentermine, norepinephrine reuptake inhibitors, obesity drugs, serendipity, serotonergic agents, thyroid extract

Summary

Joanne A. Harrold and John P.H. Wilding

Regulation of energy balance – towards rational drug design in obesity

Obesity has reached epidemic proportions across the developed world. Even though there have been numerous scientific advances in terms of the understanding of the regulation of energy homeostasis, few novel anti-obesity drugs have emerged. Furthermore, those that are available have limited efficacy in producing and maintaining a weight loss beyond 10%. This

is partly attributable to the complex neuronal circuitry at play within the central nervous system (CNS) and periphery, which acts to regulate food intake and energy expenditure. This article will focus on some of the major pathways that converge on the hypothalamus and a selection of the many products (peptides, neurotransmitters and others) expressed within the brain, that have been shown to influence energy balance. The true relevance of many of these to the regulation of human energy balance remains uncertain, but some novel anti-obesity drugs aimed at these targets are likely to emerge in the next few years.

Keywords: food intake, hypothalamus, obesity, energy homeostasis

Summary

John P.H. Wilding

Intestinal lipase inhibitors

Inhibition of fat absorption is an attractive way of managing obesity, as it will reduce intake of the most energy dense macronutrient, which has been linked to many of the long-term complications of obesity. At present this can only be achieved by malabsorptive intestinal surgery, or inhibition of intestinal lipases. Orlistat is the only intestinal lipase inhibitor that is currently available for clinical use and has been tested extensively in clinical trials. In general these show that orlistat treatment produces an average weight loss of 3.5-5kg more than placebo, and that this weight loss is associated with improvements in a wide range of cardiovascular risk factors, including cholesterol, triglycerides, glucose and blood pressure. Side effects are mainly related to inhibition of fat absorption and include loose stools and rarely faecal incontinence; they can be limited by avoidance of a very high fat diet. Studies of orlistat in patient with type 2 diabetes also show benefits in terms of glycaemic control, with an average improvement of HbA1c of about 0.4%. A four year study has also shown that orlistat can delay or prevent the progression to diabetes in people with impaired glucose tolerance.

Keywords: lipase inhibitors, orlistat, cetilistat, obesity, diabetes, clinical trials

Summary

John P.H. Wilding

Sibutramine

Sibutramine is an inhibitor of noradrenaline and serotonin and reuptake which is currently licensed for the treatment of obesity, and overweight with cardiovascular risk factors. Sibutramine is thought to reduce body weight by increasing the feeling of satiety after meals, and modifying the decline in metabolic rate which occurs during weight loss. Sibutramine has been shown to be effective in patients for weight loss in patients with both uncomplicated obesity, in patients with obesity-related hypertension and in patients with diabetes treated with a variety of oral medications. The average placebo subtracted weight loss was about 4.7 kg in a recent meta-analysis and this difference is similar in patients with type 2 diabetes and hypertension. Sibutramine has also been shown to be effective at helping weight maintenance in people who have lost weight through diet and exercise alone, diet and exercise in combination with sibutramine, and after a use of a very low calorie diet. Many cardiovascular risk factors including HDL cholesterol, triglycerides and diabetes control can be improved by sibutramine but it has been associated with modest (3-7 bpm) rises in heart rate and in some patients, small rises in blood pressure. These concerns have led to the design and conduct of a large cardiovascular outcomes trial enrolling over 9000 patients and followed for at least 4 years. Initial reports from this study show that sibutramine is well tolerated in a population at

high cardiovascular risk, with less than 5% of patients being withdrawn for rises in blood pressure during the six-week open label run-in. Sibutramine is therefore a useful addition to the pharmacotherapy of obesity and the results of this important long term outcome study are awaited with interest.

Keywords: sibutramine, obesity, cardiovascular outcomes, weight maintenance, diabetes

Muhammad Khan and John P.H. Wilding

The endocannabinoid system as a target for obesity treatment

The endocannabinoid system describes a group of arachidonic acid-derived molecules and their receptors that are widely distributed in the central nervous system and peripheral tissues. They have multiple roles including regulation of appetite, lipid metabolism and immune function. Rimonabant is an antagonist at the CB1 receptor that has been shown to reduce food intake and body weight in animals and humans, and to improve cardiovascular risk factors as a result of weight loss and its peripheral effects. Its side effects include nausea and altered mood, particularly anxiety and depression. It is licensed for clinical use in Europe, but not yet in the United States.

Summary

Owais B. Chaudhri, Kirsty L. Smith and Stephen R. Bloom

Using the body's natural signals – gut hormones

The increasing prevalence of obesity worldwide, with its attendant medical, psychological and societal consequences, has imparted renewed urgency to the search for effective treatments for obesity. Gut hormones are key physiological regulators of appetite and food intake and therefore constitute promising targets in the development of anti-obesity drugs. The neurotransmitters that mediate the control of energy intake within the central nervous system (CNS) are ubiquitous and unlike treatments that rely on manipulation of CNS circuits of appetite regulation, treatments based on gut hormones are less likely to result in disruption of unrelated neuronal pathways. Here we review the evidence for a role in control of energy balance of a number of gut peptides, with particular focus on those that are currently under development or already available as therapies.

Keywords: GLP-1, glucagon-like peptide-1, PYY(3-36), peptide YY, oxyntomodulin, ghrelin, amylin, CCK, cholecystokinin, pancreatic polypeptide, obesity, appetite, gut hormone, gut peptide

Summary

John C. Clapham and Jonathan R. Arch

Influencing energy expenditure and substrate utilisation

Many centrally acting anti-obesity drugs have been withdrawn owing to their toxicity or abuse potential. Peripherally acting thermogenic drugs offer an alternative approach. Low energy expenditure and defective fat oxidation are causes of obesity, and drugs that stimulate fat oxidation may be more effective in the long term and better for metabolism than anorectic drugs. Possible approaches include interventions in hormonal systems, uncoupling of oxidative phosphorylation, activation of AMP-activated protein kinase, and stimulation of mitochondrial biogenesis. Surprisingly, inhibitors of fatty acid and triglyceride synthesis may also alter energy balance by increasing energy expenditure.

Metabolism in the hypothalamus affects both energy intake and expenditure. In some cases a change in a metabolite concentration or enzyme activity in the periphery increases energy expenditure, but the same change centrally increases energy intake. It is therefore important to consider whether a genetically modified mouse is obese or resistant to obesity because of altered hypothalamic metabolism, and whether a centrally non-penetrant drug is required.

Keywords: obesity drugs, thermogenesis, mitochondrial biogenesis, hypothalamus, fatty acid synthesis, triacylglycerol synthesis, AMP-activated protein kinase, β_3 -adrenoceptor agonists, leptin, adiponectin, 11β -hydroxysteroid dehydrogenase, peroxisome proliferator-activated receptor δ , acetyl CoA carboxylase-2, stearoyl-CoA desaturase-1, acyl-CoA:diacylglycerol acyltransferase

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