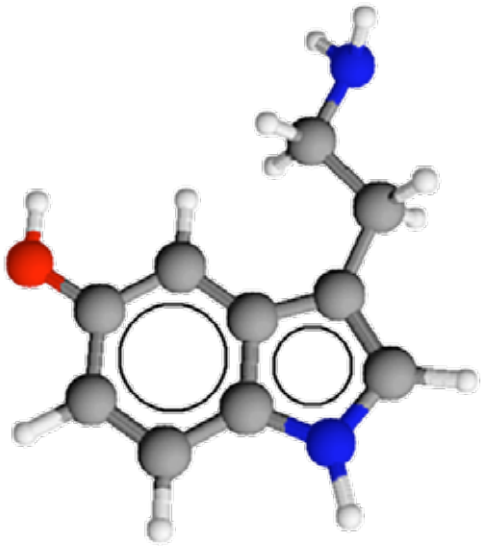
Pioneering new drug treatments for obesity



The role of the serotonin 2C receptor in modulating appetite has provided the scientific rationale for developing a new generation of anti-obesity drugs.

Obesity rates are soaring worldwide, presenting an escalating healthcare burden with huge socioeconomic cost. Research carried out by scientists at the University of Sussex and Vernalis Pharmaceuticals, on the role of the serotonin 2C receptor in modulating appetite, provided the scientific rationale for developing a new generation of anti-obesity drugs. As a result, lorcaserin, the first in its class of new serotonin 2C receptor agonists, was launched in the US in June 2013.

Overview

For years it has been known that the neurotransmitter serotonin (5-HT) is involved in the modulation of appetite and mood. In the 1980s, an early-generation drug targeting the serotonin system, the serotonin releaser and reuptake inhibitor fenfluramine, was used in Europe and the US as a treatment for obesity. Fenfluramine seemed to act by enhancing the feelings of satiety that arise after eating. However, an unacceptable side-effect profile led to its withdrawal in September 1997. This was followed by further withdrawals of anti-obesity compounds, and by 2010 only the peripheral lipase inhibitor orlistat remained, leaving a conspicuous gap in the market for drug treatments for obesity. This was, however, not the end of the serotonin system as a potential therapeutic target.

The effects of serotonin are mediated through at least 14 different receptor subtypes. Thus, the scientific challenge following the withdrawal of fenfluramine was to find a more targeted approach to drug therapy. Work in the laboratory of Professor Pete Clifton (Professor of Psychology and Head of the School of Psychology at the University of Sussex), in collaboration with Colin Dourish (Vernalis) and Larry Tecott (University of California, San Francisco), using serotonin 2C receptor 'knockout' mutant mice, provided definitive evidence that the enhancement of satiety observed with fenfluramine depended on the presence of functional serotonin 2C receptors (Vickers SP, Clifton, PG, Dourish CT et al. *Psychopharmacology* 1999; 143: 309–14).

Their work provided the rationale for the development of serotonin 2C receptor agonists as a potential treatment for obesity. Further collaborative research between Sussex and Vernalis established that serotonin 2C receptor agonists not only enhance satiety but also reduce appetite responding for food, in other words 'hunger'. Additionally, they discounted the serotonin 1B receptor as a potential target, thereby identifying serotonin 2C receptors as a very specific objective for developing therapeutic agents for obesity.

Achieving impact

The primary impact of Professor Clifton's work has been to influence research by others that has culminated in the launch of Belviq® (generic name: lorcaserin) by Arena Pharmaceuticals in the US in June 2013. Lorcaserin is a first-in-class serotonin 2C receptor agonist licensed for the treatment of obesity.

Obesity and its associated comorbidities, such as type 2 diabetes mellitus, metabolic syndrome and cardiovascular disease, present a monumental and expanding global healthcare problem. Far from being an issue that afflicts only the affluent West, this increase is also being observed in developing countries. In 2008, the WHO estimated that more than 10 per cent of the world's adult population, that is more than 1.4 billion adults, were obese and obesity rates are expected to soar by 2030. The disease burden associated with treating obesity now accounts for £5 billion of NHS spending per annum. Reversal of these trends and amelioration of their socioeconomic impact will require substantial alterations in lifestyle that includes both exercise and diet. Within this framework, however, there remains an important role for medical interventions such as drug therapy and bariatric surgery.

Work published by Professor Clifton and his colleagues in the late 1990s, including the seminal paper by Vickers et al, influenced research into a new generation of anti-obesity drugs by supporting fundraising for the initial development of serotonin 2C receptor agonists in a collaborative research programme between Vernalis and Roche. This early work attracted considerable attention and a number of other companies initiated drug development programmes in this area.

The development of lorcaserin by Arena began in the early 2000s, with the work of Professor Clifton and colleagues being heavily cited in the publication providing the key description of the drug (Thomsen WJ, Grottick AJ, Menzaghi F et al. *Journal of Pharmacology and Experimental Therapeutics* 2008; 32: 577–87). Scheduled by the US Drug Enforcement Agency in April 2013 and released on to the US market in June 2013, lorcaserin represents the first obesity treatment to have been approved by the FDA since the approval of Orlistat in 1999 and is forerunner in what may potentially be a whole new class of drugs for treating obesity.

Future impact

Research and drug development in this area continues, with other drug companies such as Bristol Myers Squibb (BMS) continuing to develop novel serotonin 2C receptor agonists. BMS, in publication of their own research, as well as many of the patent applications for these new compounds have cited several publications from Professor Clifton's laboratory.

Sussex has made a considerable commitment to translational science in recent years with investment in a new Translational Drug Discovery Group, established at the end of 2010 and directed by Professors Simon Ward and John Atack, both of whom have an extensive track record of leading industry drug discovery teams from initial ideas through to clinical trials. Combining this extensive industry experience in drug research and development with the academic excellence in basic biology research and clinical experience housed at Sussex, the Drug Discovery Group operates a novel, transdisciplinary model for drug discovery and foster cross-campus collaborations to generate new drugs for difficult-to-treat disease areas. This active commitment to translational science includes Sussex exploring the introduction of pharmacy degrees on campus, including the recruitment of a Director of Pharmacy Development. Furthermore, the expansion of drug discovery work may ultimately involve the School of Psychology in the context, for example, of drugs designed to treat mental health issues.

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